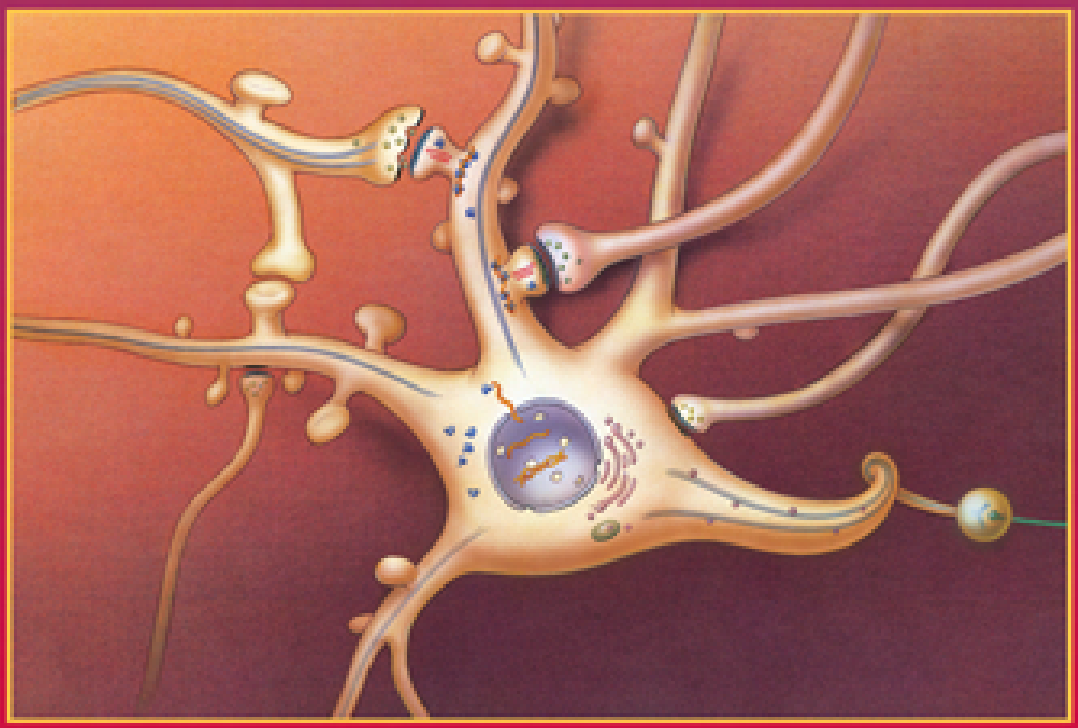
The Human Nervous System

Structure and Function

SIXTH EDITION

Charles R. Noback
Norman L. Strominger
Robert J. Demarest
David A. Ruggiero



HUMANA PRESS

VISIT…



The Human Nervous System

Structure and Function

Sixth Edition

The Human Nervous System

Structure and Function

Sixth Edition

Charles R. Noback, PhD

Professor Emeritus
Department of Anatomy and Cell Biology
College of Physicians and Surgeons
Columbia University, New York, NY

Norman L. Strominger, PhD

Professor
Center for Neuropharmacology and Neuroscience
Department of Surgery (Otolaryngology)
The Albany Medical College
Adjunct Professor, Division of Biomedical Science
University at Albany Institute for Health and the Environment
Albany, NY

Robert J. Demarest

Director Emeritus
Department of Medical Illustration
College of Physicians and Surgeons
Columbia University, New York, NY

David A. Ruggiero, MA, MPhil, PhD

Professor
Departments of Psychiatry and Anatomy and Cell Biology
Columbia University College of Physicians and Surgeons
New York, NY

HUMANA PRESS TOTOWA, NEW JERSEY

© 2005 Humana Press Inc.
999 Riverview Drive, Suite 208
Totowa, New Jersey 07512

www.humanapress.com

All rights reserved. No part of this book may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, microfilming, recording, or otherwise without written permission from the Publisher.

All papers, comments, opinions, conclusions, or recommendations are those of the author(s), and do not necessarily reflect the views of the publisher.

This publication is printed on acid-free paper. ∞
ANSI Z39.48-1984 (American Standards Institute)
Permanence of Paper for Printed Library Materials.

Production Editor: Tracy Catanese

Cover design by Patricia F. Cleary

Cover Illustration: The cover illustration, by Robert J. Demarest, highlights synapses, synaptic activity, and synaptic-derived proteins, which are critical elements in enabling the nervous system to perform its role.
Neural information derived from sensory receptors, both outside and within the body, activate the spines of the dendrites. As a consequence, neural information is communicated, via the dendrites, to the nucleus of the neuron. This activates the genomic system to release mRNA, which is transported by ribosomes, to the spines. This enables each spine to generate synaptic-specific proteins for the neuron.

For additional copies, pricing for bulk purchases, and/or information about other Humana titles, contact Humana at the above address or at any of the following numbers: Tel.: 973-256-1699; Fax: 973-256-8341; E-mail: orders@humanapr.com; or visit our www.humanapress.com

Photocopy Authorization Policy:
Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Humana Press, provided that the base fee of US $30.00 per copy is paid directly to the Copyright Clearance Center at 222 Rosewood Drive, Danvers, MA 01923. For those organizations that have been granted a photocopy license from the CCC, a separate system of payment has been arranged and is acceptable to Humana Press Inc. The fee code for users of the Transactional Reporting Service is: [1-58829-039-5/05 $30.00].

eISBN: 1-59259-730-0

Printed in the United States of America. 10 9 8 7

Library of Congress Cataloging in Publication Data
Library of Congress Cataloging-in-Publication Data

The human nervous system : structure and function / Charles R. Noback ...[et al.].-- 6th ed.
p. cm.
Previous ed. cataloged under: Noback, Charles Robert, 1916-.
Includes bibliographical references and index.
ISBN 1-58829-039-5 (hardcover : alk. paper) -- ISBN 1-58829-040-9 (pbk. : alk. paper)
1. Neurophysiology. I. Noback, Charles Robert, 1916- Human nervous system.
QP361.H85 2005
612.8--dc22

2004018287

Dedication

This book is dedicated to

Peter, Elizabeth, Norma, and Teddy Noback; Sarah and Evan Bracken; Jessica, William, and Nathan Strominger; Robert and Steven Demarest; Nancy O'Donnell; Anke Lunsmann Nolting and members of the Ruggiero, Mirra, Nolting, von Holsten, Mahler-Welch, and Tanya-Datoek families.

Preface

This sixth edition represents the combined efforts of three neuroscientists and a medical illustrator to succinctly present the fundamental principles of the organization, structure, and function of the human nervous system.

The book is intended to meet the basic needs primarily of (1) medical and dental students who want to get a general overview of this discipline; (2) beginning students in the allied health sciences and psychology students who need an introductory yet reasonably comprehensive survey of the subject; (3) residents in neurology, neurosurgery, and neuroradiology who wish to review this subject matter; and (4) readers with a background in biology who want to gain an understanding of some general concepts and specific details.

The text is designed so that the student who is first exposed to neuroscience can get an organized view of the bewilderingly complex human nervous system. The illustrations have been specifically prepared for this book to simplify and clarify items in the text. Clinical correlations and relevant symptoms from lesions are integrated in the text to elucidate important features of the substrate of the brain, spinal cord, and peripheral nervous system. Two chapters specifically deal with "Lesions of the Spinal Nerves" and "Spinal Cord and Lesions of the Brainstem." Each chapter contains a list of selected references as a guide to readers who wish to pursue topics in greater detail. It is anticipated that students who wish further information on specific areas will use the references as a starting point for online searches, which are now readily available. The book incorporates many of the significant recent advances made in neurobiology and molecular biology during the last several years. Information on the dynamics of the dendritic spines, basic neurophysiology, development and growth of the nervous system, auditory and vestibular systems, neurotransmitters as the chemical messengers of certain circuits and pathways, and basal ganglia and extrapyramidal system have been substantially expanded and revised. In addition, some 24 new drawings have been added.

We wish to thank numerous students and colleagues for their many invaluable comments and input. We wish to thank Drs. Krystal Archer-Arroyo, Anthony Cacace, Peter Greene W. Michael King, Lois Laemle; Martha Welch, Sara Glickstein, and Adele, Robert, and Mitchell Strominger, Yuansheng Tan, and Jed Peterson of Albany Medical College, class of 2006, for their efforts on our behalf. We would also like to thank Dr. David Carpenter for his many courtesies.

We thank the people at Humana Press for their patience and good will. It has been a pleasure working with them. We especially want to acknowledge Ms. Donna Niethe for her painstaking efforts in bringing the illustrations into the digital age.

Charles R. Noback
Norman L. Strominger
David A. Ruggiero
Robert J. Demarest

Introduction and Terminology

Divisions of the Nervous System
Orientation in the Brain
Organization of Neurons in the Central Nervous System: Brain and Spinal Cord

Most students feel a baffling uncertainty when beginning the study of neuroanatomy. Not until many of the facets of the subject blend in the latter half of the course, do they feel in control over the material. To ameliorate the uncertain feeling, the text and figures in the first five chapters (especially Chap. 1) should be perused for a general understanding only, then used later for reference. Chapters 8 through 13 give basic information about pathway systems, as well as background knowledge for the remaining chapters in the book.

It deserves mention that the nervous system functions together with the endocrine system in harmonizing the many complex activities of the body. The former is a rapid coordinator, whereas the latter is more deliberate in its action.

DIVISIONS OF THE NERVOUS SYSTEM

The nervous system essentially exhibits a bilateral symmetry with those structural features and pathways located on one side of the midline also found on the other side. It is subdivided anatomically into the *central nervous system* and the *peripheral nervous system* and functionally into the *somatic nervous system* and the *autonomic (visceral) nervous system*.

The *central nervous system* (CNS) comprises the brain and spinal cord. The brain is encapsulated within the skull and the spinal cord is at the center of the vertebral column. The *peripheral nervous system* (PNS) consists of the nerves emerging from the brain (called cranial nerves) and from the spinal cord (called spinal nerves). The peripheral nerves convey neural messages from (1) the sense organs and sensory receptors in the organism inward to the CNS and from (2) the CNS outward to the muscles and glands of the body.

The *somatic nervous system* consists of those neural structures of the CNS and PNS responsible for (1) conveying and processing conscious and unconscious sensory *(afferent)* information, vision, pain, touch, unconscious muscle sense from the head, body wall, and extremities to the CNS and (2) motor *(efferent)* control of the voluntary (striated) muscles. The *autonomic nervous system* is composed of the neural structures responsible for (1) conveying and processing sensory input from the visceral organs (e.g., digestive system and cardiovascular system) and (2) motor control of the involuntary (smooth) and cardiac musculature, and of glands of the viscera. Many authors, however, consider the autonomic nervous system to be exclusively concerned with visceral motor activities.

Sensory signals originating in sensory receptors are transmitted through the nervous system along sensory pathways, e.g., pain and temperature pathways and visual pathways. These signals may reach consciousness or may be utilized at unconscious levels. Neural messages for motor activity are conveyed through the nervous system to the muscles and glands along motor pathways. Both the sensory (ascending) and motor (descending) pathways include processing centers (e.g., ganglia, nuclei, laminae, cortices) for each pathway located at different anatomic levels of the spinal cord and brain. The processing centers are the computers of these complex high-speed systems. From receptors in the body

to the highest centers in the CNS, each sensory pathway system follows, in a general way, a basic sequence: (1) sensory receptors (e.g., touch corpuscles of Meissner in the skin), transmit along (2) nerve fibers to (3) processing centers in the spinal cord and brain, whence signals are conveyed by (4) other nerve fibers, which may ascend on the same side of the CNS or may cross the midline (decussate) and ascend on the opposite side of the CNS before terminating in (5) higher processing centers; from these centers (6) other nerve fibers ascend on the same side before terminating in (7) the highest processing centers in the cerebral cortex. Differences in the basic sequence are present in some ascending systems. In a general way, the motor systems are organized (1) to receive stimuli from the sensory systems at all levels of the spinal cord and brain, and (2) to convey messages via motor pathways to neuromuscular and neuroglandular endings at muscle and gland cells in the head, body, and extremities. The motor pathways comprise (1) sequences of processing centers and their fibers conveying neural influences to other processing centers within the CNS, and (2) the final linkages extending from the CNS via motor nerves of the PNS to muscles and glands.

ORIENTATION IN THE BRAIN

The long axis through the brain and spinal cord is called the *neuraxis*. It is shaped in the form of a T, with the vertical part being a line passing through the entire spinal cord and brainstem (medulla, pons, and midbrain) and the horizontal part being a line extending from the frontal pole to the occipital pole of the cerebrum (**Fig. I.1**). In essence, the long axis of the cerebrum is oriented at right angles to the long axis of the brainstem-spinal cord. The term rostral ("toward the beak") means in the direction of the cerebrum. Caudal means in the direction of the coccygeal region. These terms are used in relation to the neuraxis. In this usage, the cerebrum is rostral to the brainstem and the frontal pole of the cerebrum is rostral to the occipital lobe. Horizontal sections through the brainstem are parallel to the neuraxis. Horizontal sections through the cerebrum are cut from the frontal pole to the occipital pole, parallel to a plane passing through both eyes. Horizontal sections through the brainstem and spinal cord are cut rostrocaudally, parallel to the front and back of the neuraxis. A midsagittal or median sagittal section is cut in a vertical plane along the midline; it divides the CNS into symmetric right and left halves. Parasagittal sections are also in the vertical plane, but lateral to the median sagittal section. A coronal section of the cerebrum is cut at a right angle to the horizontal plane. An axial section of the brainstem and spinal cord is cut perpendicular to the neuraxis, giving a cross section or transverse section (*see* **Figs. 7.5** and **13.10**). Afferent (or -petal, as in centripetal) refers to bringing to or into a structure such as a nucleus; afferent is often used for sensory. Efferent (or -fugal, as in centrifugal) refers to going away from a structure such as a nucleus; efferent is often used for motor.

ORGANIZATION OF NEURONS IN THE CENTRAL NERVOUS SYSTEM: BRAIN AND SPINAL CORD

The central nervous system (CNS) comprises gray matter and white matter. *Gray matter* consists of neuronal cell bodies, dendrites, axon terminals, synapses, and glial cells, and is highly vascular. *White matter* consists of bundles of axons, many of which are myelinated, and oligodendrocytes; the white color is imparted by the myelin. It lacks neuronal cell bodies and is less vascular than gray matter.

Groupings of neuronal cell bodies within the gray matter are variously known as a nucleus, ganglion, lamina, body, cortex, center, formation, or horn. A cortex is a layer of gray matter on the surface of the brain. Two major cortices are recognized: cerebral and cerebellar cortices. The superior and inferior colliculi of the midbrain and the hippocampal formation also form cortex-like structures. The gray matter, when examined under a microscope, resembles a tangle of nerve and glial processes, called neuropil; this is actually a functionally organized entanglement of processes. Bundles of nerve fibers, many myelinated, are given such special names as *tract, fasciculus, brachium, peduncle, lemniscus, commissure, ansa,* and *capsule*. A *commissure* is a bundle of fibers crossing the midline at right angles to the neuraxis; it usually interconnects similar structures of the two sides of the brain,

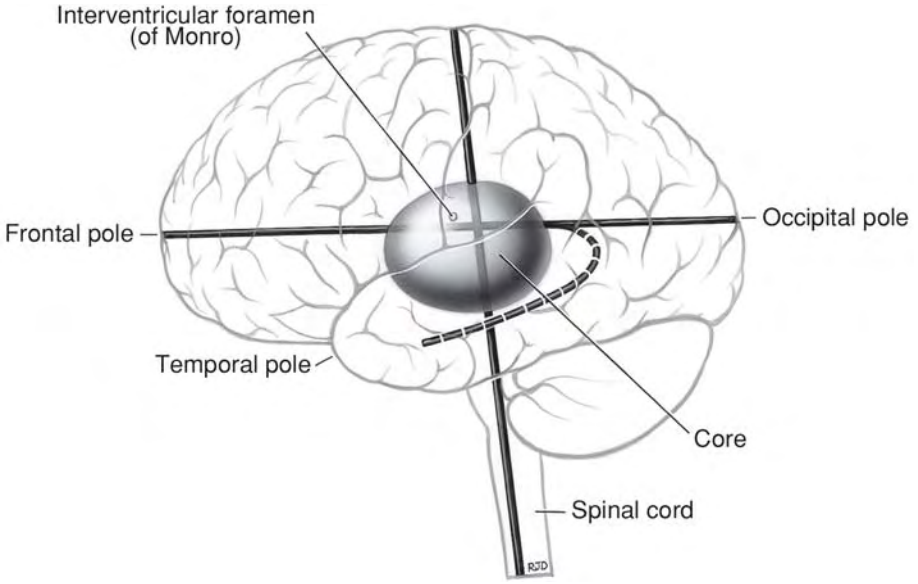


Figure 1: Geometry of the brain. Vertical axis is parallel to the long axis of the brainstem and spinal cord. Horizontal axis is parallel to the cerebrum from frontal pole to occipital pole. The broken arched line illustrates the curving of some structures of the horizontal axis during development exemplified here by the laterally positioned temporal lobe. Core structures along the horizontal axis such as the diencephalon depicted in the drawing are straight. Arching structures that follow a curve include the lateral ventricles, fornix, and hippocampus, among others (*see* **Figs. 1.7** and **5.3**).

but sometimes is merely a location where fibers decussate en-route to dissimilar locations.

Contralateral refers to the opposite side; it is used primarily to indicate, for example, that pain or paralysis occurs on the side opposite to that of a lesion. *Ipsilateral*, or *homolateral*, refers to the same side; it is used primarily to indicate, for example, that pain or paralysis occurs on the same side as that of a lesion. A *modality* refers to the quality of a stimulus and the resulting forms of sensation (e.g., touch, pain, sound, vision). Some pathways (tracts, nuclei, or areas of cortex) are *somatotopically (topographically)* organized; specific portions of these structures are associated with restricted regions of the body. For example, (1) fibers conveying position sense from the hand are in definite locations within the posterior columns (sensory pathway), and (2) certain areas of the motor cortex regulate movements of the thumb. Some structures of the visual pathway are topographically related to specific regions within the retina (retinotopic organization), and similarly some structures of the auditory pathways are organized functionally with respect to different frequencies or tones (tonotopic organization).

Measurements and Dimensions

The following information is provided for readers who may not have backgrounds in biological or physical sciences. Linear measurements and dimensions generally are given in microns or micrometers (μm) (1 μm equals one-millionth of a meter) or nanometers (nm) (1 nm or millimicron equals one-billionth of a meter). About 240,000 μm equal one inch.

As a reference, the following are the dimensions of some non-neural structures: human ovum, 100 μm; cross-section of a skeletal muscle fiber, 10-100 μm; erythrocytes, 8–10 μm; bacteria, 0.1–8 μm; and viruses, 0.15–0.5 μm.

Cell bodies of neurons range from 4–140 μm in diameter, nerve fibers (axis cylinders and sheaths) 1 or 2–20 μm diameter, chemical synapses 20–30 nm, synaptic vesicles 20–120 nm and ribosomes are about 15 nm.

Contents

Dedication v
Preface vii
Introduction and Terminology ix

1 Gross Anatomy of the Brain 1
2 Neurons and Associated Cells 11
3 Basic Neurophysiology 41
4 Blood Circulation 77
5 Meninges, Ventricles, and Cerebrospinal Fluid 89
6 Development and Growth of the Nervous System 101
7 The Spinal Cord 129
8 Reflexes and Muscle Tone 141
9 Pain and Temperature 155
10 Discriminative General Senses, Crude Touch, and Proprioception 177
11 Motoneurons and Motor Pathways 193
12 Lesions of the Spinal Nerves and Spinal Cord 207
13 Brainstem: *Medulla, Pons, and Midbrain* 219
14 Cranial Nerves and Chemical Senses 243
15 Neurotransmitters as the Chemical Messengers of Certain Circuits and Pathways 267
16 Auditory and Vestibular Systems 285
17 Lesions of the Brainstem 305
18 Cerebellum 315
19 The Visual System 329
20 Autonomic Nervous System 349
21 Hypothalamus 371
22 The Reticular Formation and the Limbic System 387
23 Thalamus 405
24 Basal Ganglia and Extrapyramidal System 419
25 Cerebral Cortex 439
Index 463

1
Gross Anatomy of the Brain

Subdivisions of the Brain
Cerebrum
Brainstem: Midbrain, Pons, and Medulla

The average human brain weighs about 1500 g (3 lbs) or approximately 2% of the body weight of a 150-lb adult. The brain, a gelatinous mass, is invested by a succession of three connective tissue membranes called *meninges* and is protected by an outer capsule of bone, the *skull*. The brain floats in cerebrospinal fluid, which supports it and acts as a shock absorber in rapid movements of the head. The major arteries and veins supplying the brain lie among the meninges.

SUBDIVISIONS OF THE BRAIN

The major subdivisions of the brain *(encephalon)* are derived from vesicles (small bladderlike fluid-filled structures) present in the embryo. They are the *telencephalon, diencephalon, mesencephalon, metencephalon*, and *myelencephalon* (**Fig. 6.7**). The telencephalon develops into the *cerebral hemispheres*, the diencephalon into the *diencephalon* (between brain), the mesencephalon into the *midbrain*, the metencephalon into the *pons* and *cerebellum* and the myelencephalon into the *medulla oblongata* (shortened to *medulla*) (**Fig. 1.1**).

The brain is divided into the cerebrum, brainstem, and cerebellum. The term *cerebrum* is generally used to include the paired cerebral hemispheres and the diencephalon. The *brainstem* comprises the midbrain, pons, and medulla. The cerebellum is located dorsal to the pons. The lower brainstem (pons and medulla) is called the *bulb* or *bulbar region.* These subdivisions are summarized in **Table 1.1**.

On the basis of the location of the tentorium (the double layer of inner dura mater located between the cerebellum and cerebral hemispheres) (**Fig. 5.1**), the brain is separated into *supratentorial* and *infratentorial* divisions. Thus, the diencephalon is supratentorial in location, whereas the brainstem is infratentorial.

The ventricular system (Chap. 5) is a continuous series of cavities within the brain filled with cerebrospinal fluid (CSF). It is subdivided as follows: The paired *lateral ventricles* are the cavities of the telencephalon (cerebral hemispheres); the *third ventricle*, a median structure, is within the diencephalon; the tubelike

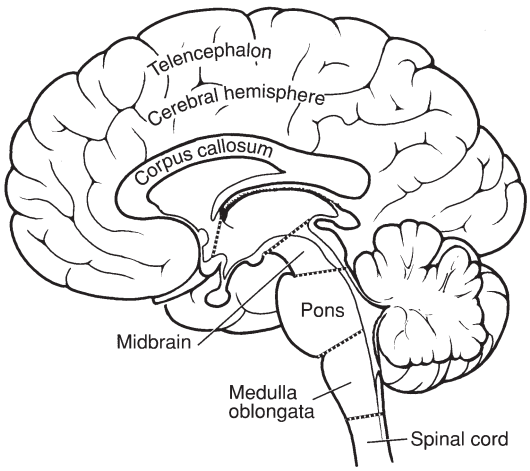


Figure 1.1: The major subdivisions of the central nervous system viewed in the sagittal section.

Table 1-1: Subdivisions of the Brain and Their Antecedents

Telencephalon Diencephalon	Cerebrum
Mesencephalon (midbrain) Metencephalon (pons portion) Myelencephalon (medulla)	Brainstem
Metencephalon (roof portion)	Cerebellum

cerebral aqueduct of Sylvius is the midbrain portion, and the *fourth ventricle* is within the pons and rostral medulla (**Figs. 5.1, 5.3,** and **5.4**). The ventricular system continues through the caudal medulla and spinal cord as the *central canal*, which terminates without outlet in the coccygeal segments of the latter.

CEREBRUM

The *cerebrum* includes the paired cerebral hemispheres, a small median segment (derived from the telencephalon) and the diencephalon. The *cerebral hemispheres* consist of the cerebral cortex (gray matter), underlying white matter, corpus striatum (gray matter, see later), corpus callosum, anterior commissure, hippocampal formation, and the amygdala (**Figs. 1.2** to **1.7**). The *corpus callosum* is a massive commissure and the *anterior commissure* is a small commissure consisting of nerve fibers that interconnect the cortices of the two hemispheres (**Figs. 1.1** and **1.5** to **1.7**). The *hippocampal formation* and *amygdala* are structures of the limbic system (**Fig. 1.7**). The unpaired median portion of the telencephalon is a small region in the vicinity of the lamina terminalis and adjacent hypothalamus.

Cerebral Topography

The hemispheres are marked on the surface, by slitlike incisures called *sulci* (**Figs. 1.2** to **1.7**). The term *fissure* is sometimes used to designate a particularly deep and constant sulcus. The raised ridge between two sulci is a gyrus. The cortex lining a sulcus is considered part of the adjacent gyrus. The hemispheres are separated from one another in the midline by the *longitudinal fissure* (**Fig. 1.4**). Each hemisphere is conventionally divided into six *lobes*: frontal, parietal, occipital, temporal, central (insula), and limbic (**Figs. 1.3** and **1.7**). The portion of the frontal, parietal and temporal lobes that overlie the insula is called the operculum.

Lobes. The lobes are delineated from each other by several major sulci, including the lateral sulcus of Sylvius, central sulcus of Rolando, cingulate sulcus, and parietooccipital sulcus. The *lateral sulcus* is a deep furrow that extends posteriorly from the basal surface of the brain along the lateral surface of the hemisphere, to terminate usually as an upward curve within the inferior part of the parietal lobe (**Figs. 1.2** and **1.3**). The *central sulcus* of Rolando extends obliquely from the region of the lateral sulcus across the dorsolateral cerebral surface and, for a short distance, onto the medial surface (**Figs. 1.2** to **1.7**). The *cingulate sulcus* is a curved cleft on the medial surface extending parallel to the curvature of the corpus callosum. The *parietooccipital sulcus* is a deep cleft on the medial surface located between the central sulcus and the occipital pole (**Fig. 1.7**).

The boundaries of the lobes on the lateral cerebral surface are as follows: (1) The frontal lobe is located anterior to the central sulcus and above the lateral sulcus; (2) the occipital lobe is posterior to an imaginary line parallel to the parietooccipital sulcus, which is on the medial surface; (3) the parietal lobe is located posterior to the central sulcus, anterior to the imaginary parietooccipital line, and above the lateral sulcus and a projection toward the occipital pole before it takes an upward curve; (4) the temporal lobe is located below the lateral sulcus and anterior to the imaginary parietooccipital line; and (5) the central lobe is located at the bottom (medial surface) of the lateral sulcus of Sylvius, which is actually a deep fossa (depression). It can be seen only when the temporal and frontal lobes are reflected away from the lateral sulcus.

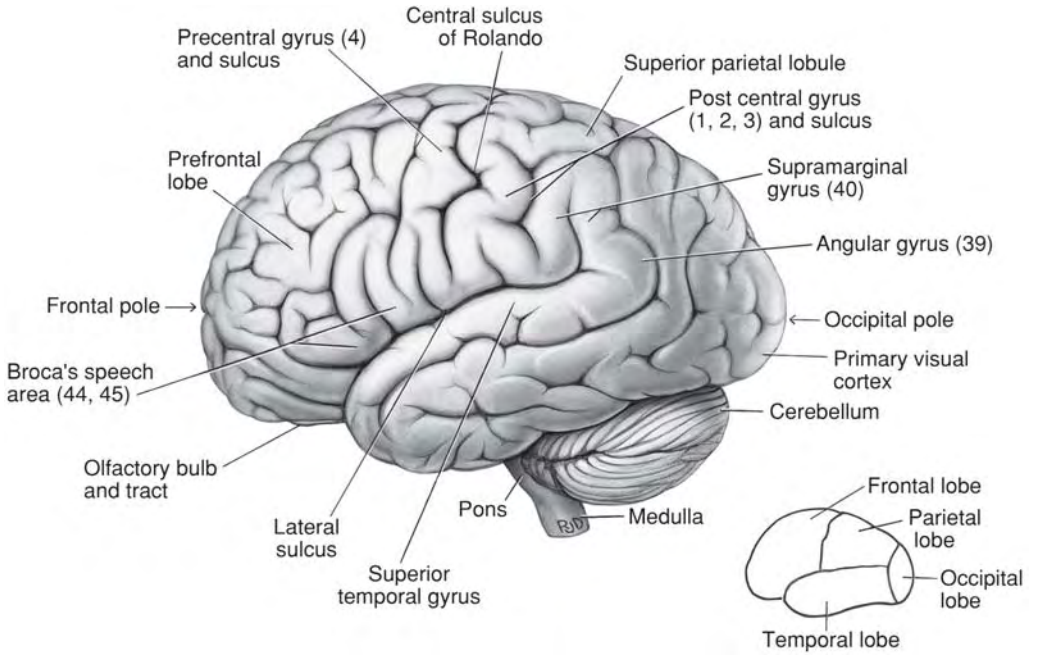


Figure 1.2: Lateral surface of the brain. Numbers refer to Brodmann's areas shown in Fig. 25.5 and 25.6.

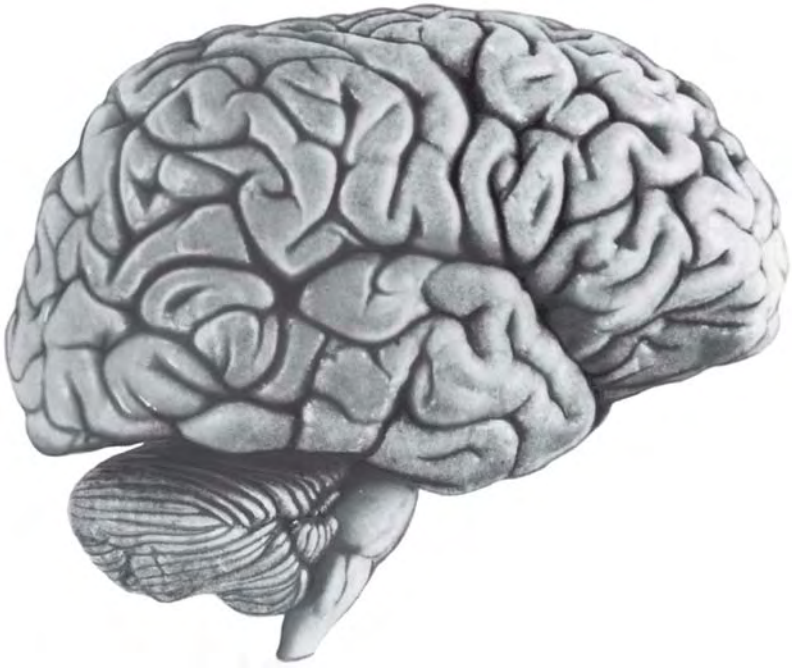


Figure 1.3: Photograph of the lateral surface of the brain. Figure 1.2 can be used to identify surface structures. (Courtesy of Dr. Howard A. Matzke.)

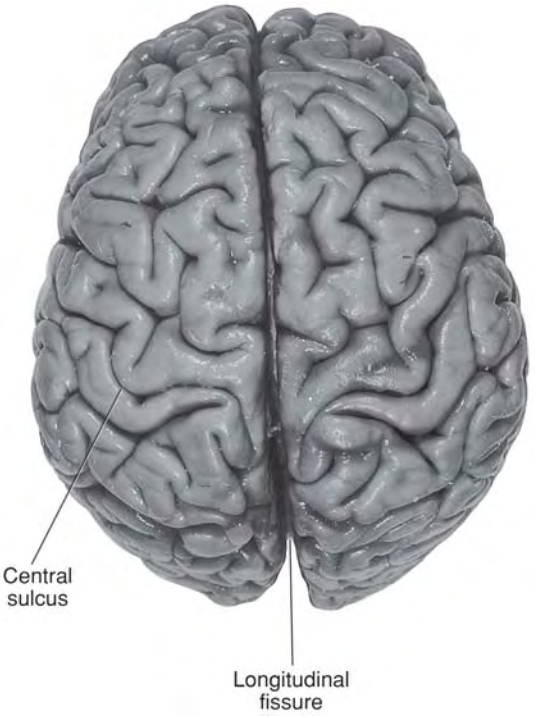


Figure 1.4: Photograph of the dorsal surface of the cerebrum. Figure 1.2 can be used to identify some of the gyri and sulci. (Courtesy of Dr. Howard A. Matzke.)

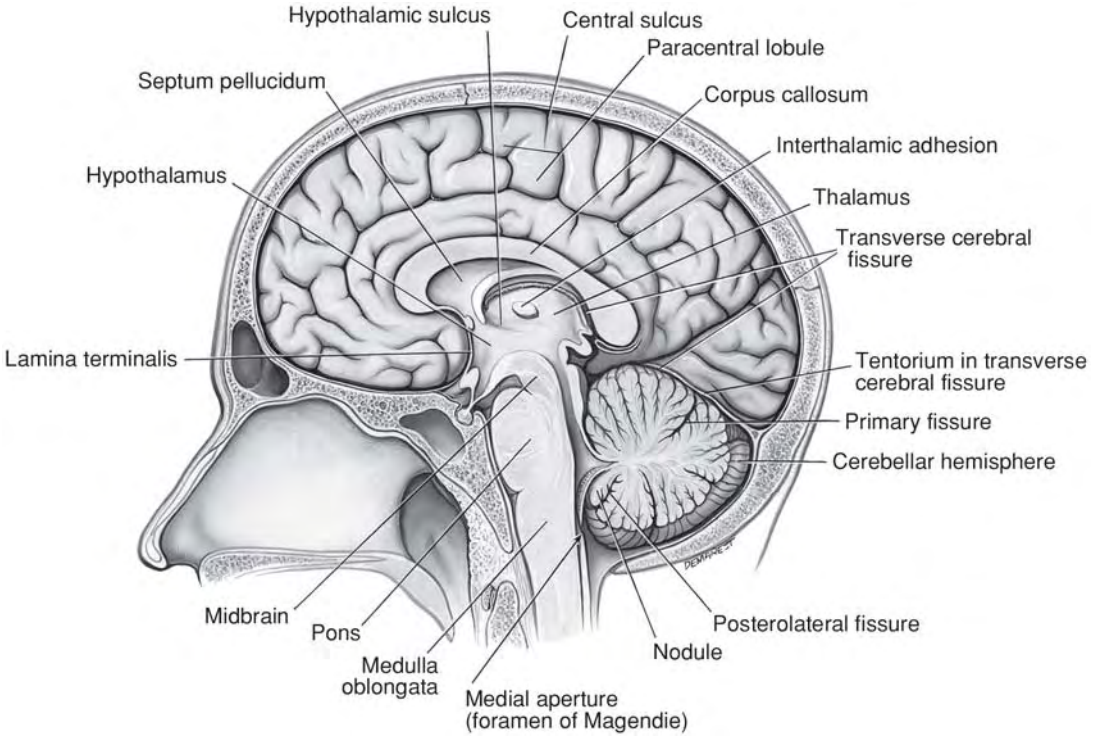


Figure 1.5: Midsagittal section of the brain.

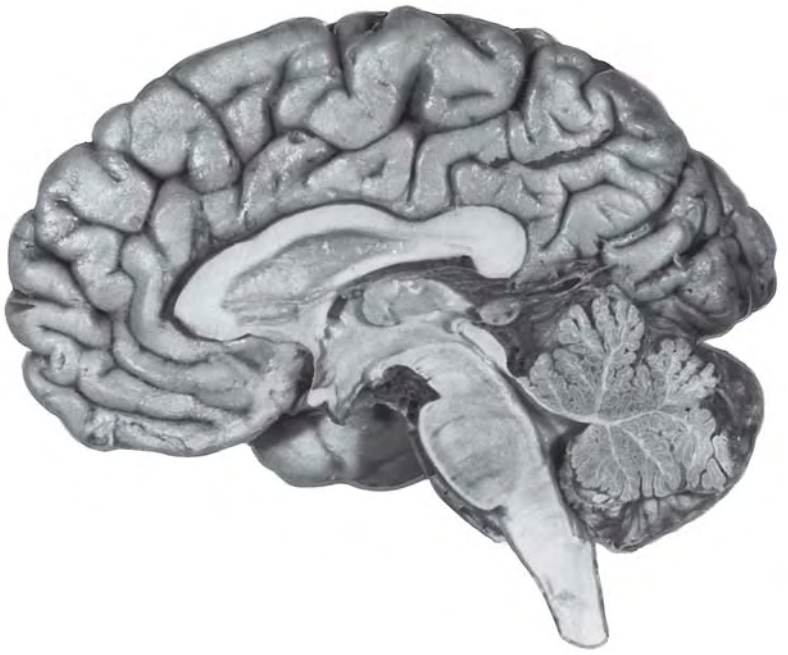


Figure 1.6: Photograph of the midsagittal section of the brain. Figures 1.5 and 1.7 can used for identifying structures. (Courtesy of Dr. Howard A. Matzke.)

The boundaries of the lobes on the medial cerebral surface (**Fig. 1.7**) are as follows: (1) The frontal lobe is located rostral to a line formed by the central sulcus; (2) the parietal lobe is between the central sulcus and the parietooccipital sulcus; (3) the temporal lobe is located lateral to the parahippocampal gyrus; (4) the occipital lobe is posterior to the parietooccipital sulcus; and (5) the limbic lobe is a synthetic one formed by parts of the frontal, parietal, and temporal lobes. It is located central to the curved line formed by the cingulate sulcus and the collateral sulcus (the latter is located lateral to the parahippocampal gyrus). The limbic lobe is the ring (limbus) of gyri bordered by this line; it includes the subcallosal area, cingulate gyrus, parahippocampal gyrus, hippocampus, dentate gyrus, and uncus (**Figs. 1.7** and **1.9**).

Gyri. The *precentral gyrus* is anterior and parallel to the central sulcus of Rolando. The *postcentral gyrus* is posterior and parallel to the central sulcus. The paracentral lobule, on the medial surface, is continuous with the precentral and postcentral gyri on the lateral surface and is partially divided by the central sulcus (**Figs. 1.5 to 1.7**).

The cortex anterior to the central sulcus is motor in function; that posterior to the central sulcus is sensory in function. The postcentral gyrus and the posterior part of the paracentral lobule are known as Brodmann areas 1, 2, and 3 of the cerebral cortex (**Figs. 25.5** and **25.6**). The posterior part of the precentral gyrus and adjacent portion of the paracentral gyrus are called area 4 or the motor cortex. The *transverse gyri of Heschl, located* in the upper part of the temporal lobe on the floor of the lateral sulcus, make up the primary receptive areas for audition (areas 41 and 42). The cortex on either side of the calcarine sulcus is the primary receptive area for vision (area 17). The areas outside the primary receptive areas are called *association areas*; Broca's area (**Fig. 1.4**), for example, is a cortical area associated with the formulation of

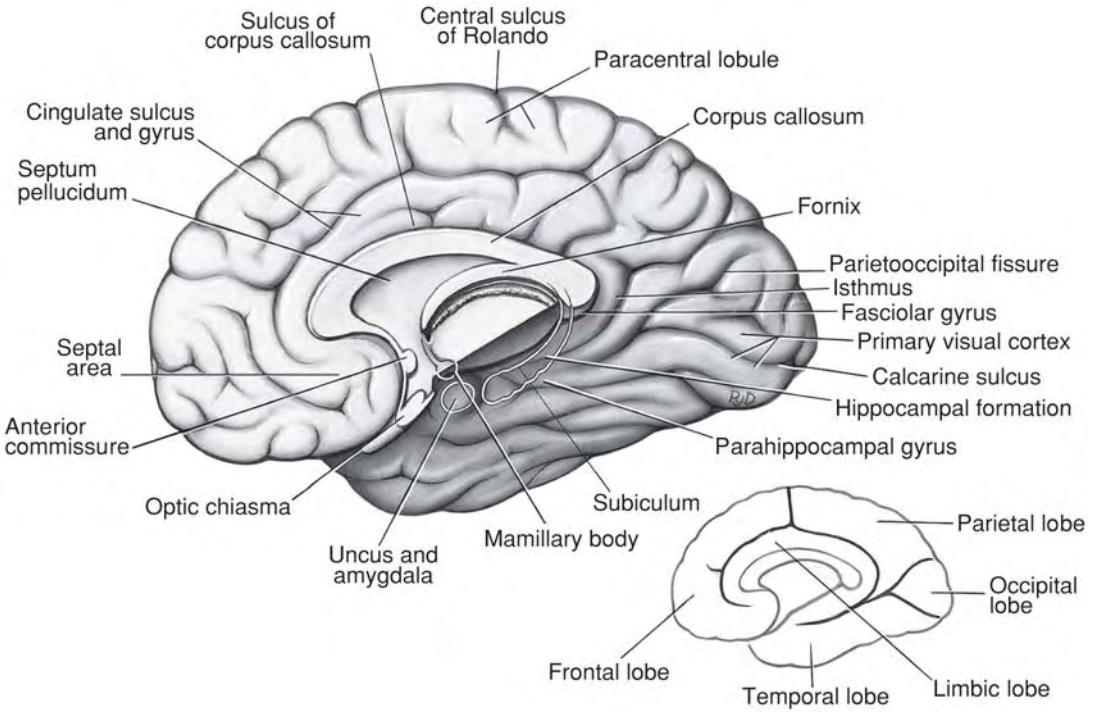


Figure 1.7: Medial surface of the cerebral hemisphere. The limbic lobe consists of the cingulate gyrus, isthmus, and parahippocampal gyrus. White lines represent the amygdala and the hippocampal formation. The amygdala is located within the uncus. The hippocampal formation (hippocampus and dentate gyrus) is located in the floor of the temporal horn of the lateral ventricle (*see* Fig. 1.9).

speech. The functional aspects of the Brodmann areas are discussed in Chapter 25.

Basal Ganglia

The term *basal ganglia* refers to several subcortical nuclei together with a nucleus of the diencephalon and a couple in the midbrain (**Figs. 1.8** and **24.2** and **Table 1.2**). These are the caudate nucleus, lenticular nucleus, subthalamic nucleus, and substantia nigra. No longer included are the claustrum and amygdala (amygdaloid body or amygdaloid nucleus); the latter is a component of the limbic system (Chap. 23). The *caudate nucleus* and the *lenticular nucleus* are collectively called the *corpus striatum*; they are the deep nuclei of the cerebral hemispheres. The *lenticular nucleus* is subdivided into the *putamen* and *globus pallidus* (pallidum, paleostriatum). The *putamen* and the *caudate nucleus* are called the *striatum* (neostriatum). The *subthalamic nucleus* is located within the ventral thalamus (Chap. 23). The *substantia nigra* is a nucleus located within the midbrain (Chap. 13).

Diencephalon

The *diencephalon*, located in the ventromedial portion of the cerebrum, is continuous caudally with the midbrain (**Fig. 1.1**). It consists of four subdivisions: epithalamus, thalamus (dorsal thalamus), hypothalamus, and ventral thalamus (subthalamus). The epithalamus, choroid

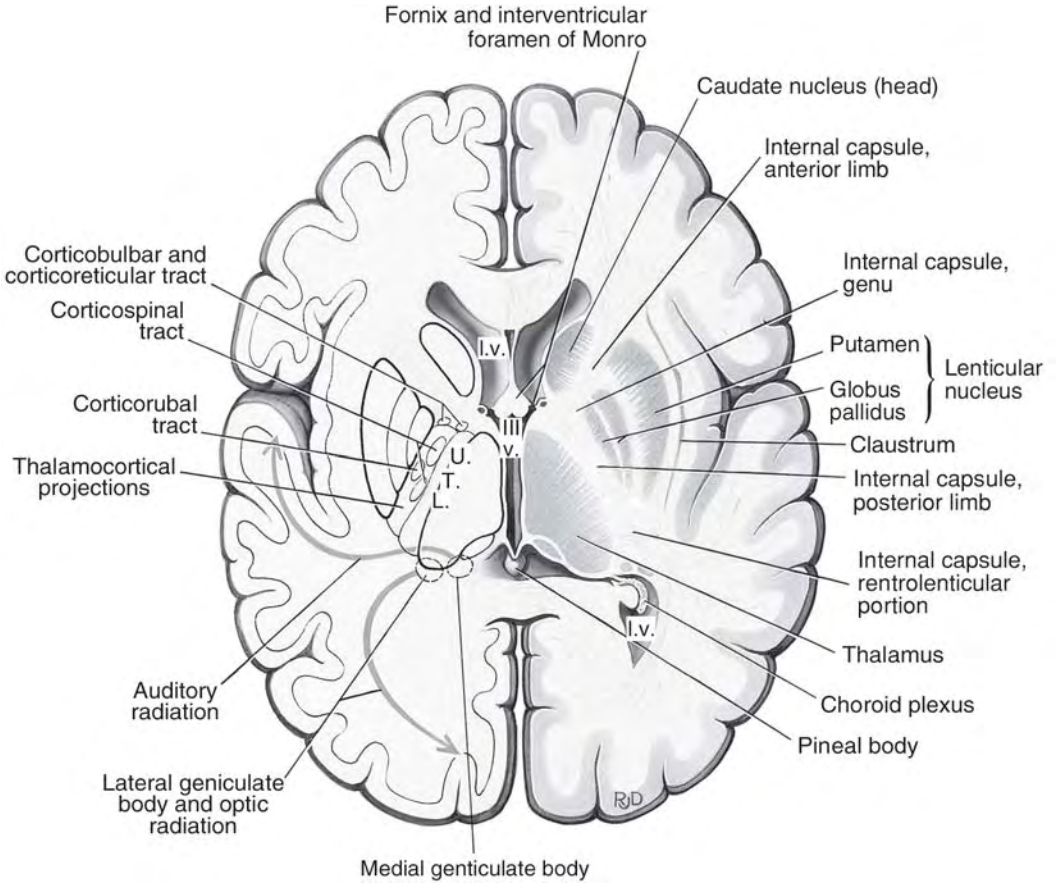


Figure 1.8: Horizontal section through the cerebrum. Note the location of the head of the caudate nucleus, lenticular nucleus, thalamus relative to the ventricles, and the internal capsule. Some constituents of the internal capsule are indicated on the left side, where the topographic distribution of the motor pathways from motor cortex is indicated; U, upper extremity; T, trunk; L, lower extremity.

plexus of the third ventricle (**Fig. 1.5**), and the pineal body (**Fig. 1.8**) form the upper margin (roof) of the diencephalon. Ventral to the thalamus is the hypothalamus, which includes the mamillary bodies, and the hypophysis (pituitary gland) (**Figs. 1.5** and **1.9**). The ventral thalamus is located lateral to the hypothalamus.

Internal Capsule

The *internal capsule* is a massive bundle of nerve fibers, which contains almost all of the fibers projecting from the subcortical nuclei to the cerebral cortex and from the cerebral cortex to subcortical structures in the cerebrum, brainstem, and spinal cord (**Fig. 13.4**). It is divided into an anterior limb, genu, and posterior limb (**Fig. 1.8**). Retrolenticular and sublenticular parts of the posterior limb are recognized (**Figs. 1.8** and **23.3**). The *anterior (caudatolenticular) limb* is located between the caudate nucleus and the lenticular nucleus. The *genu* (knee) is located between the anterior and posterior limbs. The *posterior (thalamolenticular) limb* is located between the thalamus and lenticular

Table 1-2: The Basal Ganglia

Lenticular nucleus		
Globus pallidus	Striatum	Corpus striatum
Putamen		
Caudate nucleus		
Subthalamic nucleus		
Substantia nigra		

Note: See Tables 24-1 and 24-2 for more complete details.

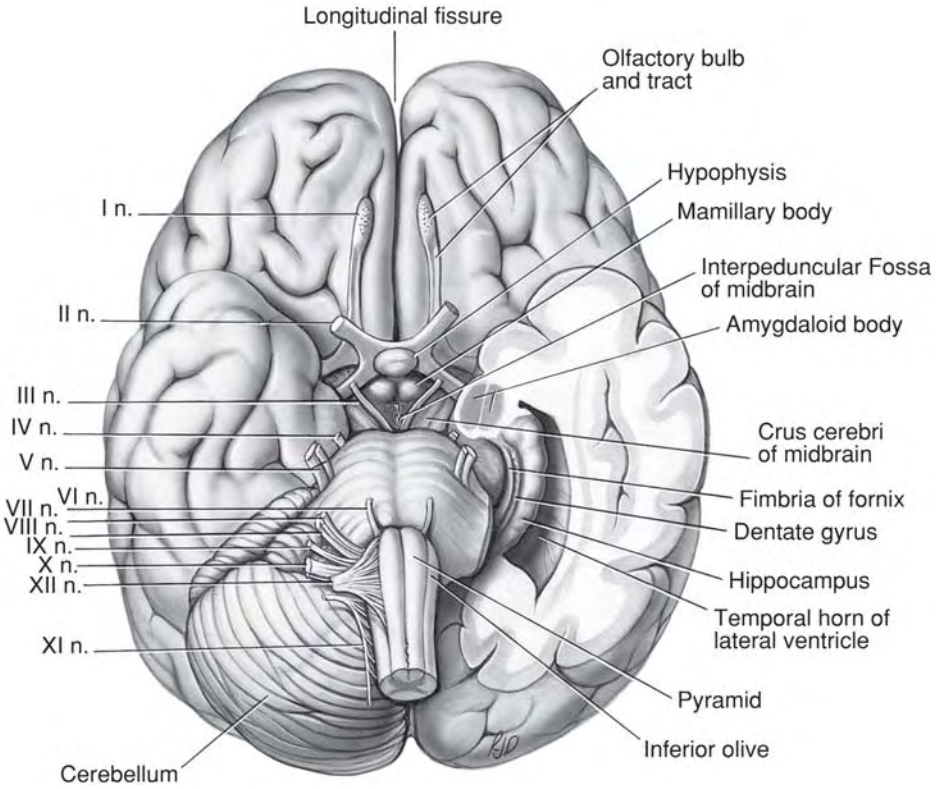


Figure 1.9: Basal surface of the brain. Note roots of the cranial nerves. A horizontal section through the right temporal and occipital lobes reveals the hippocampus, dentate gyrus, fimbria of the fornix, and temporal horn of the lateral ventricle. The fimbria of the fornix consists of fibers entering the fornix from the hippocampus. The hypophysis and the mammillary body are components of the diencephalon. n, cranial nerve.

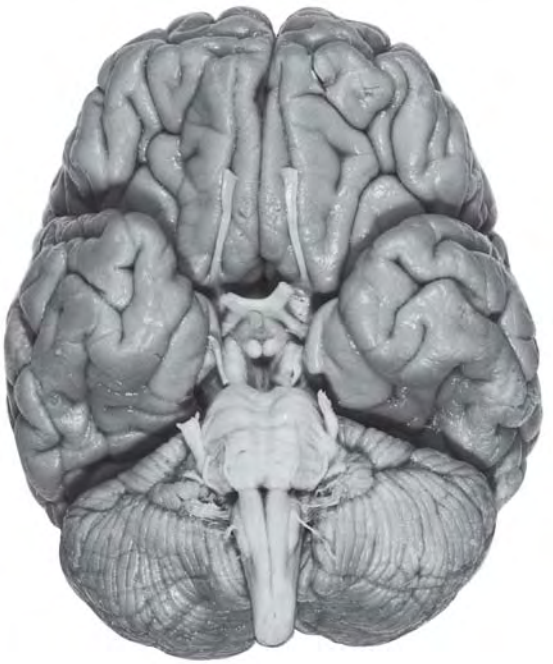


Figure 1.10: Photograph of the basal surface of the brain. Figures 1.9 and 13.4 can be used for identification. (Courtesy of Dr. Howard A. Matzke.)

nucleus. The *retrolenticular (postlenticular)* part of the posterior limb is located lateral to the thalamus and posterior to the lenticular nucleus and the *sublenticular part* is ventral to the lenticular nucleus.

BRAINSTEM: MIDBRAIN, PONS, AND MEDULLA

Several prominent landmarks are present on the anterior surface of the brainstem (**Figs. 1.9, 1.10,** and **13.4**). In the midbrain, the paired cerebral peduncles (crus cerebri) are lateral to the interpeduncular fossa through which passes the *oculomotor nerve (third cranial nerve*). The *superior* and *inferior colliculi* form four protuberances on the posterior surface of the midbrain; the trochlear nerve (fourth cranial nerve) emerges from the brainstem immediately caudal to the latter (**Figs. 13.2** and **13.3**). The *trigeminal nerve (fifth cranial nerve*, composed of a small motor root and a large sensory root) emerges on the lateral aspect of the massive pons. The pyramids, olives, and roots of seven cranial nerves are features visible on the anterior surface of the medulla. The *pyramids* are formed by the fibers of the pyramidal tracts (corticospinal tract). The *olive* is a protuberance formed by the inferior olivary nucleus (**Figs. 13.3 to 13.5**). From medial to lateral, the *abducent (sixth), facial (seventh)*, and *vestibulocochlear (eighth) nerves* emerge at the junction of the pons and medulla. The *glossopharyngeal (ninth)* and *vagus (tenth) nerves* emerge as a series of rootlets from the sulcus on the posterior margin of the olive. The *spinal accessory (eleventh) nerve* emerges in the form of rootlets from the medulla and from the spinal cord (between the dorsal and ventral roots of the first six cervical spinal nerves). The *hypoglossal (twelfth) nerve* emerges from the sulcus between the olive and pyramid (**Fig. 1.9**).

Note that the third, sixth, and twelfth cranial nerves emerge from the anterior brainstem in a longitudinal line just lateral to the midsagittal plane. The fifth, seventh, ninth, tenth, and eleventh cranial nerves emerge from the lateral aspect and the trochlear from the posterior aspect of the brainstem (**Fig. 13.2**). For a more complete description of the surface anatomy of the brainstem, *see* Chapter 13.

SUGGESTED READINGS

Agur AM, Dalley AF II. *Grant's Atlas of Anatomy.* 11th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.

Beatty J. *The Human Brain: Essentials of Behavioral Neuroscience.* Thousand Oaks, Ca.: Sage, 2001.

Benarroch E. *Medical Neurosciences: An Approach to Anatomy, Pathology, and Physiology by Systems and Levels.* Philadelphia, PA: Lippincott Williams & Wilkins; 1999.

Brodal A. *Neurological Anatomy in Relation to Clinical Medicine.* 3rd ed. New York, NY: Oxford University Press; 1991.

Brodal P. *The Central Nervous System: Structure and Function.* 3rd ed. New York, NY: Oxford University Press; 2004.

Burt A. *Textbook of Neuroanatomy.* Philadelphia, PA: Saunders; 1993.

Clemente CD. *Anatomy: A Regional Atlas of the Human Body.* 4th ed. Baltimore, MD: Williams & Wilkins; 1997.

England MA, Wakely J. *Color Atlas of the Brain & Spinal Cord: An Introduction to Normal Neuroanatomy.* St. Louis, MO: Mosby Year Book; 1991.

Felten D, Józefowicz R, Netter F. *Netter's Atlas of Human Neuroscience.* Teterboro, NJ: Icon Learning Systems; 2003.

Gilman S, Winans S. *Manter and Gatz's Essentials of Clinical Neuroanatomy and Neurophysiology.* 10th ed. Philadelphia, PA: FA Davis; 2003.

Haines D. Neuroanatomy: *An Atlas of Structures, Sections, and Systems.* Philadelphia, PA: Lippincott Williams & Wilkins; 2004.

Heimer L. *The Human Brain and Spinal Cord: Functional Neuroanatomy and Dissection Guide.* New York, NY: Springer-Verlag; 1995.

Kandel E, Schwartz J, Jessell T, editors. *Principles of Neural Science.* 4th ed. New York, NY: McGraw-Hill; 2000.

Kiernan JA. *Barr's the Human Nervous System: An Anatomical Viewpoint.* 7th ed. Philadelphia, PA: Lippincott-Raven; 1998.

Marshall L, Magoun H. *Discoveries in the Human Brain: Neuroscience Prehistory, Brain Structure, and Function.* Totowa, NJ: Humana; 1998.

Martin JH. *Neuroanatomy: Text and Atlas.* New York, NY: McGraw-Hill Medical; 2003.

Nolte J, Angevine JB. *The Human Brain: In Photographs and Diagrams.* 2nd ed. St. Louis, MO: Mosby; 2000.

Nolte J, Sundsten JW. *The Human Brain: An Introduction to its Functional Anatomy.* 5th ed. St. Louis, MO: Mosby; 2002.

Petras J, Noback C., eds. Comparative and Evolutionary Aspects of Vertebrate Central Nervous System. *Ann. NY Acad. Sci.* 1969;167:1–573.

Purves D, GJ Augustine, D Fitzpatrick, WC Hall, A-S LaMantia, JO McNamara, et al., eds. *Neuroscience.* 3rd ed. Sunderland, MA: Sinauer Associates; 2004.

Riley HA. *An Atlas of the Basal Ganglia, Brainstem and Spinal Cord.* Baltimore: Williams and Wilkins; 1943.

Rowland LP, ed. *Merritt's Neurology.* Philadelphia, PA: Lippincott Williams & Wilkins; 2000.

Schnitzlien H, Murtaugh F. *Imaging Anatomy of the Head and Spine: A Photographic Color Atlas of MRI, CT, Gross, and Microscopic Anatomy in Axial, Coronal, and Sagittal Planes.* 2nd ed. Baltimore, MD: Urban & Schwarzenberg; 1990.

Squire LR, Bloom FE, McConnell S, Roberts JL, Spitzer NC, Zigmond MJ. *Fundamental Neuroscience.* New York, NY: Academic; 2003.

Victor M, Ropper A. *Adams and Victor's Principles of Neurology.* New York, NY: McGraw-Hill Medical; 2002.

Warwer I. *Atlas of Neuroanatomy.* Boston, MA: Butterworth-Heineman; 2001.

Williams PL. *Gray's Anatomy: The Anatomical Basis of Medicine and Surgery.* 38th ed. New York, NY: Churchill Livingstone; 1996.

Wong-Riley MTT. *Neuroscience Secrets.* Philadelphia, PA: Hanley & Belfus; 2000.

Woolsey TA, HJ, Gado MH. *The Brain Atlas: A Visual Guide to the Human Central Nervous System.* Hoboken, NJ: Wiley; 2003.

2
Neurons and Associated Cells

Neuroplasticity
Organelles and Components
Neurotrophic Factors and Tropic Factors
Structure of Peripheral Nerves and Ganglia
Neuroglia (GLIA)
Paraneurons
Nerve Regeneration
Plasticity and Axonal Sprouting

NEUROPLASTICITY

Some 100–200 billion ([1–2] $\times$ 10^{11}) neurons (nerve cells), as well as many more glial cells, are integrated into the structural and functional fabric that is the brain. They exhibit a wide diversity of form and sizes. The neuron is the basic unit of the nervous system and is composed of four structurally defined regions: *a cell body* (soma) that emits a single nerve process called an *axon,* which ends at *presynaptic terminals,* and a variable number of branching processes called *dendrites* (**Figs. 2.1** and **2.2**). Each axon, including its collateral branches, usually terminates as an arbor of fine fibers; each fiber ends as an enlargement called a *bouton*, which is part of a synaptic junction. At the other end of the neuron, there is a three-dimensional *dendritic field*, formed by the branching of the dendrites (**Fig. 2.2**).

The cell body is the genomic and metabolic center of the neuron. Dendrites are the main recipients of neural signals for communication between neurons and contain critical processing complexes (Chap. 3). The axon is the conduit for conducting messages (action potentials) to the presynaptic terminals where each neuron is in synaptic contact with other neurons and, thus, is part of the network that constitutes the nervous system. A neuron is designed to react to stimuli, to transmit the resulting excitation rapidly to other portions of the nerve cell, and to influence other neurons, muscle cells, and glandular cells. Neurons are so specialized that most are incapable of reproducing themselves and they lose viability if denied an oxygen supply for more than a few minutes.

ORGANELLES AND COMPONENTS

Each neuron consists of a large nucleus, a plasma (cell) membrane and cytoplasm consisting of cytosol (fluid phase of cytoplasm), and a number of organelles, including the endoplasmic reticulum, Nissl substance, Golgi apparatus, mitochondria, lysosomes and cytoskeleton (**Figs. 2.3 to 2.5**).

Nucleus

The nucleus is delineated from the cytoplasm by a double-layer unit membrane called the *nuclear envelope*. This membrane is perforated by *nuclear pores*, through which *macromolecules* synthesized in the nucleus pass into the cytoplasm. In humans, the nucleus contains 46 chromosomes formed from DNA (deoxyribonucleic acid) and proteins. The DNA that encodes some functions is present in the mitochondria. The *outer layer* of the nuclear envelope is continuous with the membranes of the

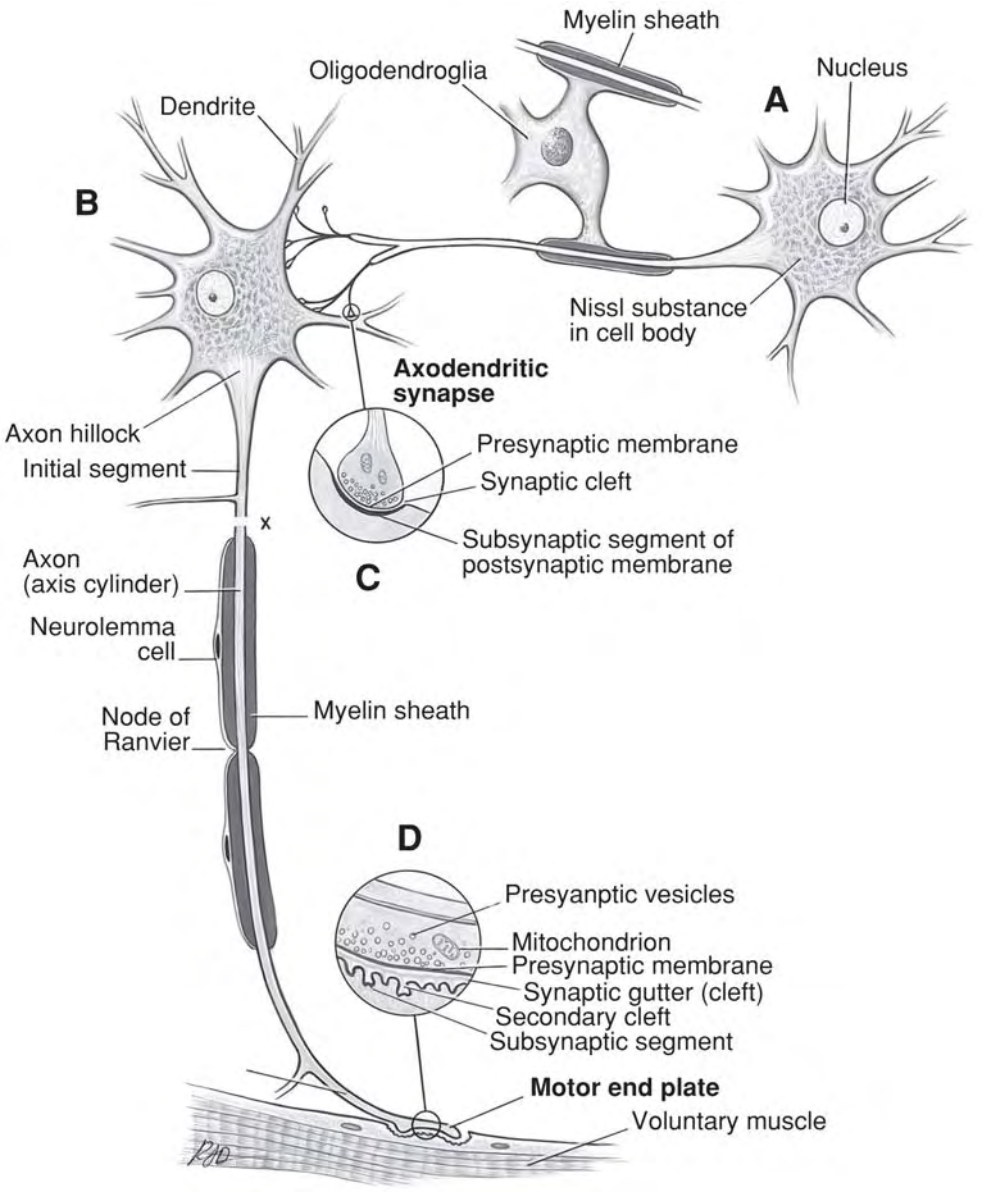


Figure 2.1: Diagram of **(A)** a neuron located wholly within the central nervous system and **(B)** a lower motoneuron located in both the central and peripheral nervous systems. The latter synapses with a voluntary muscle cell to form a motor end plate. Note the similarities, as reconstructed from electron micrographs, between **(C)** a synapse between two neurons and **(D)** a motor end plate. The X represents the border between the central nervous system (above the X) and the peripheral nervous system (below the X). The myelin sheath of neuron **(A)** is entirely the product of a glial cell, and that of neuron **(B)** is produced by a glial cell inside the central nervous system and by a Schwann (neurolemma) cell in the peripheral nervous system.

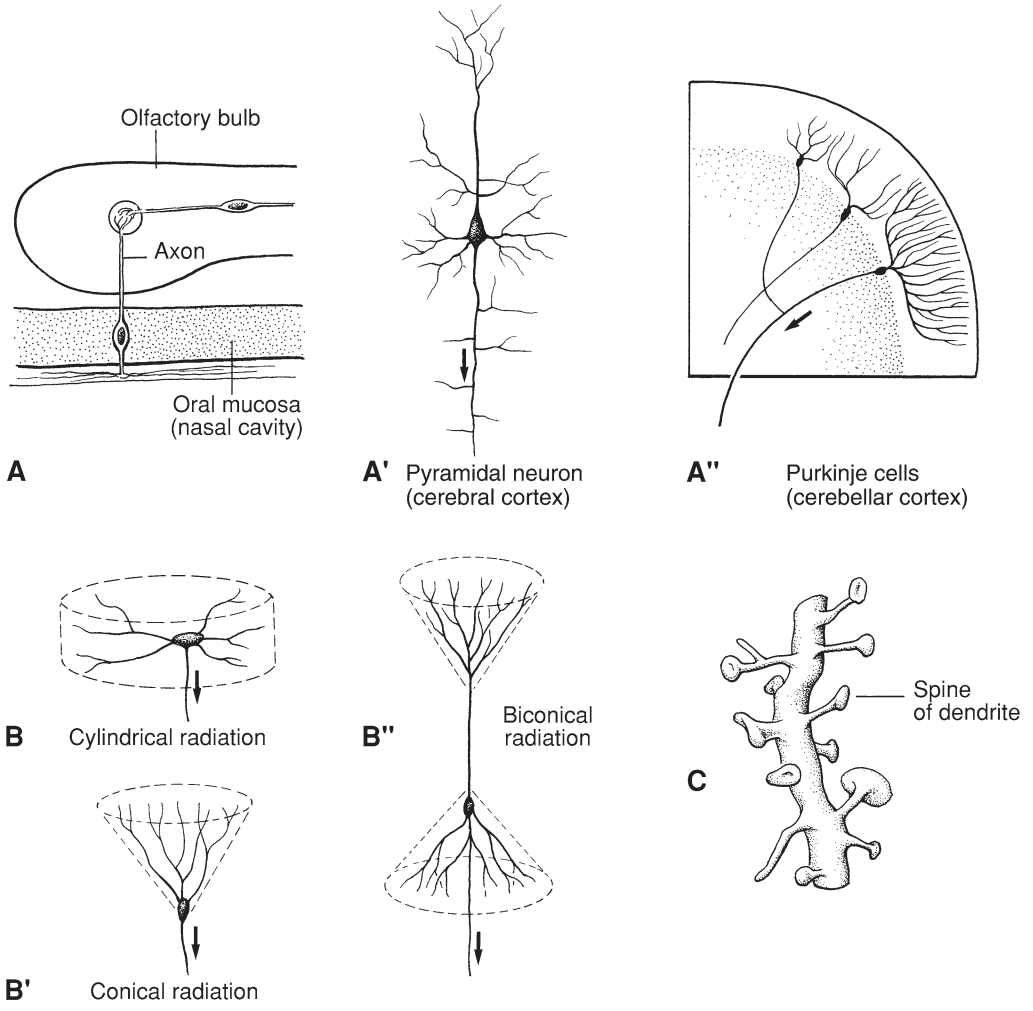


Figure 2.2: (A) The degrees of densities among dendritic arborizations are expressed as a sequence of *selective arbors* **(A),** *sampling arbors* **(A')** and *space-filling arbors* **(A")**. The *selective arbor* **(A)** of an olfactory receptor neuron (ORN) is comprised of a receptive dendritic arbor of cilia, a cell body located within the olfactory mucosa in the nasal cavity (OM), and an axon **(Ax)** that terminates in the olfactory bulb (OB) (Chap. 14). The *sampling arbor* **(A')** with its intermediate arborization pattern is in a pyramidal neuron of the *neocortex* (Chap. 25). The *space-filling arbor* **(A")** is oriented in a plane as in the dendritic branches of Purkinje neurons of the cerebellum (Chap. 18). Arrow indicates axon.

(B) Examples of some geometric shaped radiation domains of dendritic arbors. The dendritic arbor **(B)** radiates from the cell body to form a *cylindrical domain* (note axon). The dendritic arbor **(B')** radiates from the cell body to form a *cone domain*. The dendritic arbor **(B")** radiates bipolarly from the cell body to form *two-cone domains.*

(C) Outline of an electron micrograph segment of a spiny dendrite illustrating a variety of shapes and sizes of *spines* described as simple to branched and with spine heads ranging from stubby to mushroom shaped. In vivo *imaging* has demonstrated that dendritic spines (**S**) form, collapse and reform, and rapidly change size and shape in response to a diverse array of stimuli. Spine morphology is activity dependent and dynamically responsive (Chap. 3). The arrow indicates the direction of the passage of the nerve impulse of an axon. (*Adapted from Fiala and Harris, 1999).*

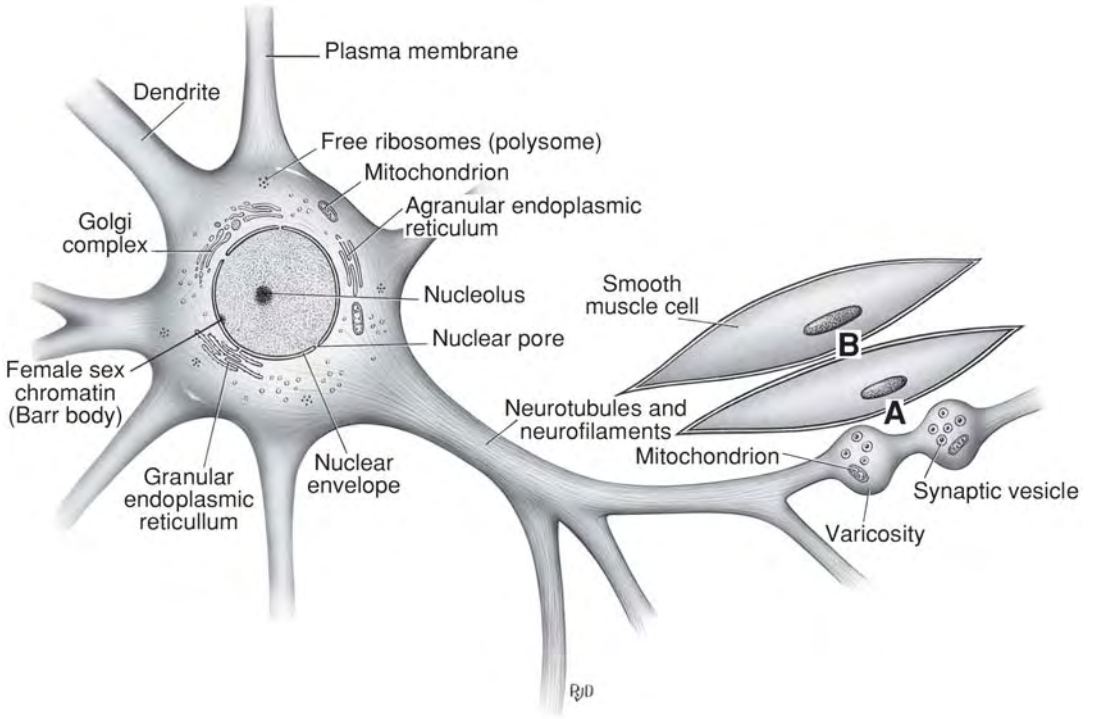


Figure 2.3: Some of the cytoplasmic organelles and associated structures of a postganglionic neuron of the autonomic nervous system. The junction between the varicosity and smooth muscle cell **A** is a typical synapse (Fig. 15.3). The junction between two smooth muscle cells **B** is an electrical synapse (gap junction, nexus). The small circles in the cell body represent lysosomes.

endoplasmic reticulum. The *inner layer* of the envelope has filaments that attach to the nuclear chromatin and to other structures involved in pore-diameter control.

The chromosomes contain sequences of DNA called genes. Through a process known as transcription, the genes determine the amino acid sequences of polypeptides and, thus, the structure and properties of proteins. The *translation* of the *DNA code* into a protein is accomplished by a special ribonucleic acid (RNA) called messenger RNA (mRNA). The mRNA migrates from the nucleus through the nuclear pores to the cytoplasm and becomes associated with a ribosome, which contains another RNA called ribosomal RNA (rRNA). The rRNA acts as a template upon which the amino acids are assembled. Another RNA, called transfer RNA (tRNA), conducts the activated amino acids in the cytosol to the messenger RNA to be synthesized into the peptide. Importantly, DNA specifies RNA through the process known as transcription. The RNA then specifies proteins via translation. Thus, the information coded into the DNA sequence of the gene is *transcribed* to the mRNA, which carries it to the ribosome, where it is translated into a specific amino acid sequence to the corresponding peptide. The ribosomes are the sites of protein synthesis.

Like other cells, each neuron synthesizes three classes of proteins, each with a specific physiological role. Except for a few proteins encoded by mitochondria, essentially all of the macromolecules of a neuron are made in the cell body from mRNAs. These three classes are as follows: (1) *Proteins synthesized in the cytosol by free ribosomes and polysomes; they*

remain in the cytosol. These proteins, distributed by slow axoplasmic transport, include enzymes essential to catalyze metabolic processes of the cytoskeleton. (2) *Proteins synthesized in the cytosol by free ribosomes and polysomes, which are incorporated into the nucleus, mitochondria, and peroxisomes*. These include enzymes that are involved in the synthesis of RNA, DNA, transcription factors regulating gene expression, and other proteins required by these organelles. Mitochondria are distributed by slow axoplasmic flow. (3) *Proteins synthesized in association with the membrane systems attached to or within the lumen of the endoplasmic reticulum and Golgi apparatus (GA)*. They are disbursed by vesicles that bud off the GA and are distributed via fast axoplasmic flow to such organelles as lysosomes and secretory (transmitter containing) vesicles and to the plasma membrane for the maintenance of its protein composition.

The prominent nucleolus within the nucleus is a ribosome-producing machine consisting largely of RNA and protein along with some DNA. It is the site of ribosomal (rRNA) production and initial assembly. The nucleolus is well developed in cells such as neurons, which are active in peptide and protein synthesis.

The brain utilizes more genes than any other organ in the body, estimated to be 30,000–40,000 genes, with about 15,000 unique to the neural tissue.

In females, nuclei of cells throughout the body, including neurons, contain a condensation of one of the two X chromosomes (sex chromatin) called a Barr body (**Fig. 2.3**). It

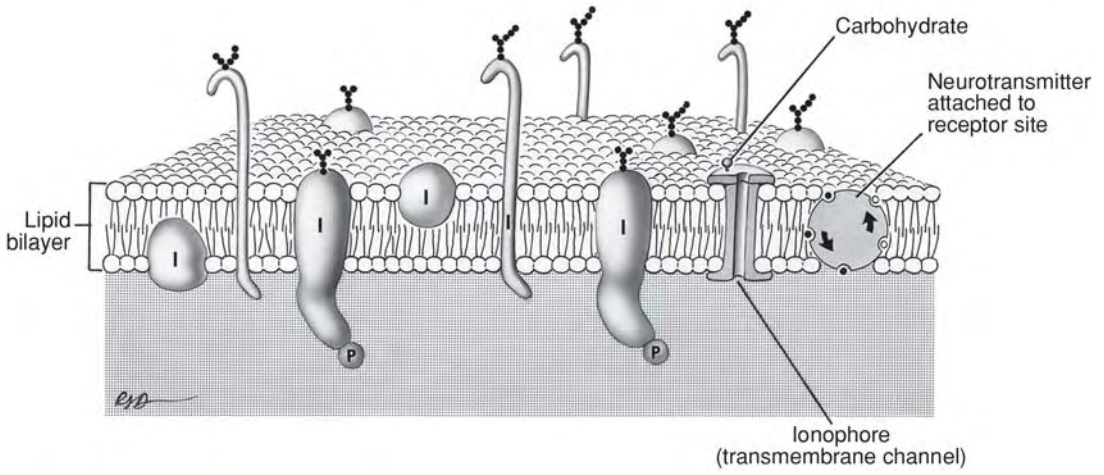


Figure 2.4: Plasma membrane of a neuron. Several types of integral proteins (I) are embedded in the bilipid layer of the 5-nm-thick plasma membrane. The carbohydrate chains of the glycoproteins are located on the outer membrane surface. The differential distribution of specific proteins is a basis for regional differences in the functional activities expressed by the membrane. The carbohydrate chains of the glycolipids are not illustrated. At right, integral proteins are schematized as (1) a transmembrane channel (ionophore) with about a 0.5-nm-wide pore and (2) a coupled sodium–potassium pump (Chap. 3). An ionophore acts as a selective channel for the preferential passage of an ion such as sodium or potassium (Chap. 3). The disk on the outer margin of the ionophore represents the receptor site (receptor protein) acting as a binding subunit for a neurotransmitter, which is represented as an irregular object above the receptor site. The pump is specialized to transport sodium ions (open circles) out of the neuron in exchange for pumping potassium ions (solid circles) into the neuron. Peripheral proteins (P) are attached to the integral proteins.

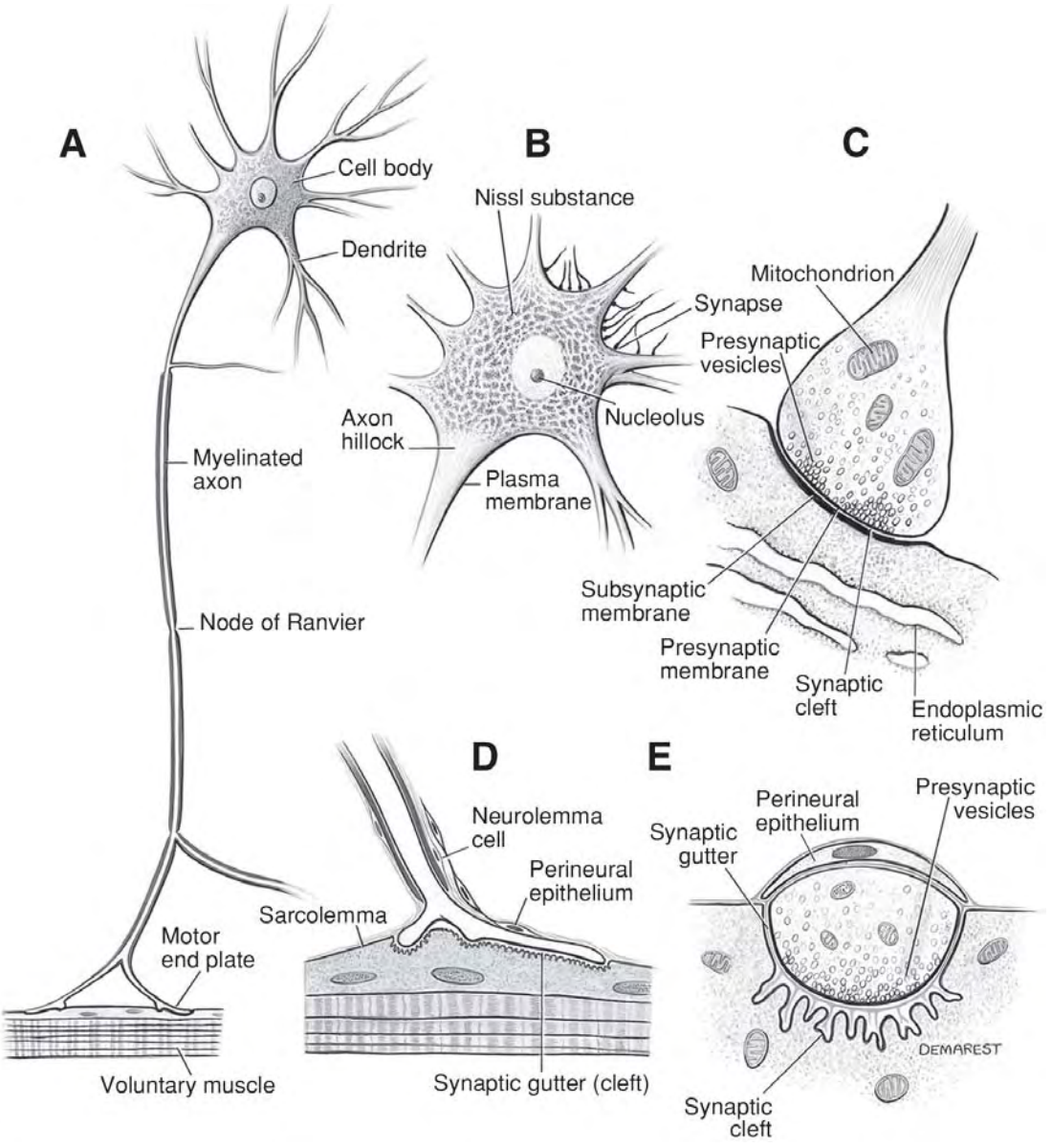


Figure 2.5: A motoneuron (lower motor neuron, alpha α motor neuron) of the anterior horn of the spinal cord. **(A)** The neuron includes a cell body and its processes (dendrites and axons). Note the axon collateral branching at a node of Ranvier. **(B)** Axons terminate as telodendria; each telodendritic terminal has a bulbous ending, forming either an axosomatic or an axodendritic synapse. **(C)** The synapse as reconstructed from electron micrographs. Note similarities between the synapse and motor end plate in **E**. **(D)** Motor end plate as visualized with the light microscope. The sarcolemma (plasma membrane of muscle cell) is the postsynaptic membrane of the motor end plate. **(E)** Section through motor end plate as based on electron micrographs. Portion of terminal ending fits into synaptic gutter of muscle fiber. Neurolemma (Schwann) cells cover the portion of axon not in the gutter. The secondary clefts (junctional folds) are modifications of the sarcolemma.

appears as a small clump near the nuclear envelope. This structure, first described in cat spinal motoneurons, can be seen in smears of cells inside the mouth (buccal smears). A normal male has an XY configuration and lacks Barr bodies.

Plasma (Cell) Membrane (Fig. 2.4)

The *plasma (cell) membrane* is a highly organized, dynamic 8- to 10-nm-thick organelle. Many cellular processes are initiated as a consequence of molecular reactions within the membrane. It is a flexible nonstretchable structure consisting of two layers of lipid molecules (bilipid layer of phospholipids) and associated proteins, lipids (cholesterol and glycolipids), and carbohydrates (**Fig. 2.4**). Its surface area can only be changed by the addition or subtraction of membrane. The lipids are oriented with their hydrophilic (polar) ends facing the outer surface and the hydrophobic (nonpolar) ends projecting to the middle of the membrane. Thus, the hydrophilic heads face the water on both sides of the membrane. The membrane proteins (peptide chains) embedded in the bilipid layer are called *integral* or *intrinsic proteins* to which *peripheral proteins* are attached. On the external side of the membrane are carbohydrate chains; those linked to proteins form *glycoproteins* and those linked to lipids form *glycolipids*. These carbohydrates can act as mediators in cell and molecular recognition and of cell adhesion. As a result, the side facing the tissue fluids differs from that facing the interior of the neuron, not only structurally but also in function.

All biologic membranes are organized (1) to block the diffusion of water-soluble molecules, (2) to be selectively permeable to certain molecules via specialized pores or channels (ionophores), and (3) to transduce information by protein receptors responsive to chemical or physical stimulation by neurotransmitters, hormones, light, vibrations, or pressure (Chap. 3). The lipid layers act as a barrier to diffusion by being impermeable to ions; the proteins are organized as specific receptors, ion channels, transporters, and carriers that make them quite permeable to particular ions under certain circumstances (Chap. 3).

There is continuous traffic of small molecules crossing the plasma membrane. This movement involves (1) the regulation of the neuron's concentration of such inorganic ions as Na^+, K^+, Ca^{2+} and Cl^- by shifting the ions in one or the other direction across the plasma membrane, (2) taking in oxygen for cellular respiration and expelling carbon dioxide, and (3) transporting nutrients into and metabolic waste products out of the cell. Some substances diffuse across the membranes from a region of higher concentration to one of lower concentration. This diffusion down the concentration gradient is called *passive transport* because the neuron does not expend energy to effect the movement. The concentration gradient represents the potential energy that powers the diffusion. Another form of passive transport is called *facilitated diffusion* because the ions and molecules diffuse across the membrane with the help of *transport proteins* that span the membrane. In this diffusion, the transport proteins apparently remain in place and help the ions across the membrane by undergoing a subtle change that translocates the binding site from one side of the membrane to the other. These changes can trigger both the binding and the release of the transported ions.

The movement of substances across a semipermeable plasma membrane from sites of low concentration to sites of high concentration ("uphill") occurs by *active transport*, *exocytosis,* and *endocytosis*. Active transport has a critical role in a neuron to maintain the internal concentration of small molecules that differ from the concentrations in the extracellular environment. The process is called *active transport* because in order to pump the molecules "uphill," the neuron must expend its own energy. Active transport is carried out by specific proteins inserted in the membrane, with adenosine triphosphate (ATP) supplying the energy. ATP powers the active transport by transferring its terminal phosphate group directly to the transport ion. This presumably induces the protein to change its configuration

in a manner that translocates the ions bound to the protein across the membrane. One such transport system is the sodium–potassium pump, an integral membrane protein, which exchanges sodium for potassium ions across the plasma membrane. This pump transport system drives the ions against steep gradients. The pump oscillates between two conformational states in a pumping cycle that translocates three Na^+ ions out of the neuron for every two K^+ ions pumped into the neuron. ATP powers the changes in conformation by transferring a phosphate group to the pump transport protein. The two conformational states differ in their affinity for Na^+ and K^+ and in the directional orienting of the ion-binding sites. Prior to phosphorylation, the binding sites face the cytoplasm and only the Na^+ sites are receptive. Sodium binding induces phosphate transfer from ATP to the pump, triggering the conformational change. In its new conformation, the pump's binding sites face the extracellular side of the plasma membrane, and the protein now has a greater affinity for K^+ than it does for Na^+. Potassium binding causes the release of the phosphate and the pump returns to its original conformation. Because the pump also acts as an enzyme that removes phosphate from ATP, it is also called ATPase.

In the process called *exocytosis*, the neuron releases macromolecules (e.g., neurotransmitters) by fusion of presynaptic vesicles with the plasma membrane and secretion of their contents to the outside (*see* Synapses at the Motor End Plate, Chap. 3). In the process called *endocytosis*, the neuron takes in macromolecules and particulate matter by forming vesicles derived from the plasma membrane (*see* Recycling of Synaptic Vesicles, Chap. 3).

Physiologically, the membrane proteins can be characterized in functional terms. These include the following:

1. *Channels (ionophores)* that allow for the passage of certain ions (such as Na^+, K^+, Cl^- and Ca^{2+}), across the membrane down concentration and voltage gradients (Chap. 3). The channels are glycoproteins surrounding continuous pores through the membrane (transmembrane) that allow some ions to flow at rates as high as 100 million ions per second per channel. Some channels are permanently open; others only transiently open. The latter are said to be "gated." When the gate opens, ions pass through the channel, and when the gate closes, ions do not pass through (Chap. 3). A calculation indicates that a chemically gated acetylcholine channel (a channel that opens in the presence of acetylcholine) will open for 1 ms and then close. During the 1 ms, about 20,000 Na^+ ions flow into the neuron, and somewhat fewer K^+ ions flow out of the neuron, through each channel.
2. *Pumps* that serve to transport certain ions (sodium–potassium pump, Chap. 3) or metabolic precursors of macromolecules. Pumps work against an ionic gradient and thus extrude Na^+ from the neuron. Energy for this activity is obtained from the hydrolysis of ATP.
3. *Receptor protein sites* are involved with the recognition of neurotransmitters and hormones. They act as binding sites for these substances on the outer surface of the plasma membrane. The sites initiate the responses of the neuron, muscle fiber, or gland cell to specific stimuli (chemical or mechanical).
4. *Transducer proteins* are involved in coupling receptors to enzymes following the binding of a ligand, such as a transmitter or a hormone, to the receptor. The term ligand refers to any molecule that binds to a receptor on the surface of a cell. Through the action of a transducer, an enzyme could initiate the action of a *second messenger* such as cyclic adenosine monophosphate (cAMP) (*see* Second Messenger–G Protein, Chap. 3).
5. *Structural proteins* are proteins that form junctions with other neurons, such as cell adhesion molecules (CAMs). Intercellular recognition between neural cells and their adhesion one to the other in functionally meaningful patterns involves glycoproteins called *neural cell adhesion molecules*

(NCAMs). These molecules are present on the cell surface of all developing neural cells, where they influence pathways of cell migration and terminal axonal outgrowths. NCAMs also have important roles in adult tissues, where they are responsible for the affinity of nerve terminals to their targets and for the interactions between neurons and other cell types. NCAMs also contribute to the general adherence property of all neural cells. Each is a glycoprotein with a high content of a carbohydrate called sialic acid. It appears that this molecule is important in promoting the outgrowth of the developing axon and is involved in responding to guidance cues during neural development (Chap. 6). The *NCAMs* and another glycoprotein family called *cadherins* form the basis of cell-specific adhesion, where identical molecules on different cells bind to each other. Another glycoprotein family called *integrins* mediates between the neuronal surface and molecules in the extracellular matrix. The NCAM is present in most neural induction and is presumed to contribute to the general adhesive properties of neural cells.

6. *Neurotransmitter transporter proteins* are plasma membrane glycoproteins involved with the uptake from the synaptic cleft of such transmitters as serotonin, dopamine, and glutamate for recycling (**Fig. 3.10**). The energy stores in the transmembrane electrochemical gradients are utilized to drive these chemical agents into the axon terminal.

The cell membrane has a dynamic fluidity in that the proteins, which are suspended in a "solution of membrane lipids," can shift laterally and even rotate within the bilipid layer unless restrained by the binding of the protein to some underlying cytoplasm.

The movement and addition of acetylcholine (ACh) receptors within the plasma membrane is a graphic example of this fluidity. ACh receptors of the plasma membrane of a muscle fiber are normally clustered and confined in the subsynaptic membrane of the motor end plate (**Fig. 2.5**). Prior to the formation of a motor end plate during early development, ACh receptors are distributed throughout the plasma membrane of the embryonic muscle fiber. Within hours following the contact of an axon with the embryonic muscle, a motor end plate begins to form. ACh receptors accumulate in the subsynaptic membrane largely by the *insertion of newly formed receptors* and by *migration of some receptors* from non-end-plate plasma. This clustering, induced by putative chemotropic factors, is accompanied by a drastic reduction of receptors on the non-end plate plasma membrane. At this stage, the muscle can no longer be innervated by another axon. If the axon is cut and the muscle denervated and allowed to degenerate, there is a reduction in the number of ACh receptors at the former end plate accompanied by their wide distribution all over the plasma membrane. If this muscle is reinnervated, the ACh receptors again accumulate in the new subsynaptic membrane and are reduced in the non-end-plate plasma membrane. Regional differences in the biochemical properties of the plasma membrane result in local functional specializations of the membrane (Chap. 3).

Nissl Bodies, Ribosomes, and Endoplasmic Reticulum

Nissl bodies (chromophilic substance) are basophilic aggregates located in the cell body and dendrites of each neuron, but absent in the axon and axon hillock located at the junction of cell body and axon (**Fig. 2.1**). Each Nissl body is composed of (1) flattened sacs (called cisternae) of *granular endoplasmic reticulum (rough ER*) studded with ribosomes facing the cytosol, (2) *free ribosomes*, and (3) clusters of ribosomes linked together, called *polysomes* (**Fig. 2.3**). Ribosomes are the intracellular organelles that carry out the protein synthesis. They are composed of several species of mRNA and a number of proteins. The granular ER is continuous with the smooth ER (ER without ribosomes). The *rough ER* is the organelle involved in the synthesis of neurosecretory proteins, integral membrane proteins of the plasma membrane, and proteins of the

lysosomes (see Golgi Apparatus later). The free ribosomes and polysomes are associated with the synthesis of the proteins of the cytosol and nonintegral proteins of the plasma membrane. The *smooth ER* is the locale where triglycerides, cholesterol, and steroids are synthesized.

Neurons require prodigious amounts of proteins to maintain their integrity and to perform their functional activities. In 1–3 days, they synthesize an amount equal to the total protein content of the neuron. Much of it is distributed within the neuron by axonal transport (*see* later). Neurons are actually neurotransmitter secretory cells rivaling glandular cells as the most prolific protein synthesizing cells.

Mitochondria and Peroxisomes

Mitochondria are membrane-bound organelles, which, as the cell's power plants, are the chief source of energy for each cell (**Fig. 2.3**). Energy, water, and carbon dioxide are the products of aerobic cell respiration and enzymatic activity, mainly of carbohydrates and, to a lesser degree, of amino acids and fats. The energy released from the oxidation of food is converted to phosphate-bound energy as ATP. ATP-bound energy is essential for several cellular processes, including the maintenance of the pumps for the transport of ions across the plasma membrane, muscle contraction, and protein synthesis (Chap. 3).

Neurons, unlike most cells, lack the ability to store glycogen as an energy source. As a consequence, they are dependent for their energy on circulating glucose and oxygen. Glucose is the substrate utilized by mitochondrial enzyme systems of neurons for the aerobic generation of ATP. (Neurons do not utilize fat as a substrate for the process of anaerobic generation of ATP.) This explains why we lose consciousness if the blood supply to the brain is interrupted for a short time.

The mitochondria have a small amount of their own DNA (mtDNA), which enable them to produce some constituent proteins, RNA, and enzymes. Many substances required by the mitochondria are derived from the cytoplasm.

Several developmental neurological disorders, called *mitochondrial myopathies*, have been attributed to the inheritance of mtDNA abnormalities. Such a congenital myopathy is myoclonic epilepsy with ragged red fibers (with special stains, abnormal mitochondria appear red, hence ragged red fibers). Myopathies are conditions in which the symptoms are the result of the dysfunction of muscle but with no evidence of nerve degeneration. Mitochondria are present in the ovum but not in sperm. Thus, mtDNA inheritance is said to be matrilineal and independent of nuclear inheritance.

Peroxisomes are organelles that function to detoxify, with the enzyme catalase, by hydrolyzing hydrogen peroxide, thereby protecting the neuron from this chemical agent.

Lysosomes

Lysosomes are membrane-bound vesicles that act as an intracellular digestive system. They contain a variety of hydrolytic enzymes that digest and degrade substances originating both inside and outside of the neuron. The hydrolytic enzymes and lysosome membranes are synthesized in the rough ER and then transferred to the GA for further processing. After budding from the GA, these products are transported via vesicles to the lysosomes. The digested materials include many cell components such as receptors and membranes, some of which can be recycled. The so-called yellow lipofuscin granules found in neurons of advanced age are said to represent the effects of "wear and tear" and could be insoluble residues of lysosomal activity.

Golgi Apparatus (GA)

The GA is a complex organelle composed of stacks of flattened cisternal sacs, vesicles, and membranous tubules (**Fig. 2.3**). Newly ER-synthesized protein molecules move through the ER tubules and then bud off into vesicles that are transported to the GA and sequentially through several cisternal compartments. While passing through, the proteins are modified and sorted out before finally emerging from the GA

by budding off the cisternal membranes as vesicles containing glycoproteins and secretory products. These glycoproteins are then dispersed to their destinations via plasmic transport as (1) the integral proteins of the plasma membrane, (2) the secretory proteins packaged into secretory vesicles that are released in response to an external signal, and (3) enzymes of the lysosomes. Each membranous vesicle budded from the GA apparently has external molecules that recognize "docking sites" on the surface of the specific organelle to which they are destined to join.

Cytoskeleton: Neurotubules and Neurofilaments

Adaptation to various shapes (and to carry out coordinated and directed movements) is dependent on complex internal scaffolds of protein filaments and tubules and their associated proteins called the *cytoskeleton.* The cytoskeletal network extends throughout the cell body, dendrites, and axon. The cytoskeleton is not a fixed structure but undergoes changes during development and growth and after injury.

The cytoskeleton consists of numerous fibrillar organelles called (1) *neurotubules (microtubules)*, each roughly 20–25 nm in diameter, (2) *neurofilaments (microfilaments)*, roughly 10 nm in diameter, and (3) *actin microfilaments*, about 5 nm in diameter. The tubules and filaments comprise about 25% of the total protein of a neuron. Neurotubules and neurofilaments are found throughout the cytoplasm. As molecular motors, they mediate movement of organelles by transport. The actin microfilaments, primarily located close to the plasma membrane, are critical organelles in growth cones (Chap. 6). These tubules and filaments are of variable length with no single element extending the entire length of an axon or dendrite. The tubules are polar structures. Within an axon, the so-called plus end of each tubule is oriented toward the axon terminus and the minus end is oriented toward the cell body (**Fig. 2.6**). In a dendrite, the polarities of the tubules are mixed, with about half having the plus end oriented toward the cell body and the other half with the minus end oriented toward the cell body. The tubules and filaments consist of a polymer of repeating subunits that are in a dynamic state of flux, continuously growing longer or shorter.

Neurotubules are unbranched cylinders composed of polymers of the protein *tubulin*. They are involved in the transport of membranous organelles throughout the neuron. *Neurofilaments* are unbranched cylinders formed by actin and other proteins. The neurofilament proteins, found only in neurons, are members of a family of proteins that include intermediate filament proteins seen in other cells and a protein in glial cells called *glial fibrillary acidic protein* (*GFAP).*

The special properties of these cytoskeletal elements enable them to undergo transitions from stable to dynamic structures. In the fully differentiated neurons the cytoskeleton gives each neuron and its processes (axon and dendrites) (1) mechanical strength and (2) via its neurotubules, the tracks to transport materials between the cell body and its axon terminals. A highly plastic cytoskeleton is exhibited during the development of a neuron or in nerve regeneration following the transection of a peripheral nerve. In these situations, growth cones utilize the cytoskeleton to elongate, retract or rapidly change their shape and to act as mobile sensors (Chap. 6, **Fig. 6.4**).

Axonal Transport (Axoplasmic or Axon Transport or Axoplasmic Flow)

The distribution of many substances from the cell body throughout the neuronal processes and from the processes to the cell body is carried out by *axonal transport.* It is called *anterograde* or *orthograde axonal transport* when the direction of movement is away from the cell body into the dendrites and axon and *retrograde axonal transport* when the direction is from the dendrites and axon toward the cell body. Transport comprises two general rates, which occur in all dendrites and axons: (1) a *fast rate* with movement of 200–400 mm per day and (2) a *slow rate* of about 1–5 mm

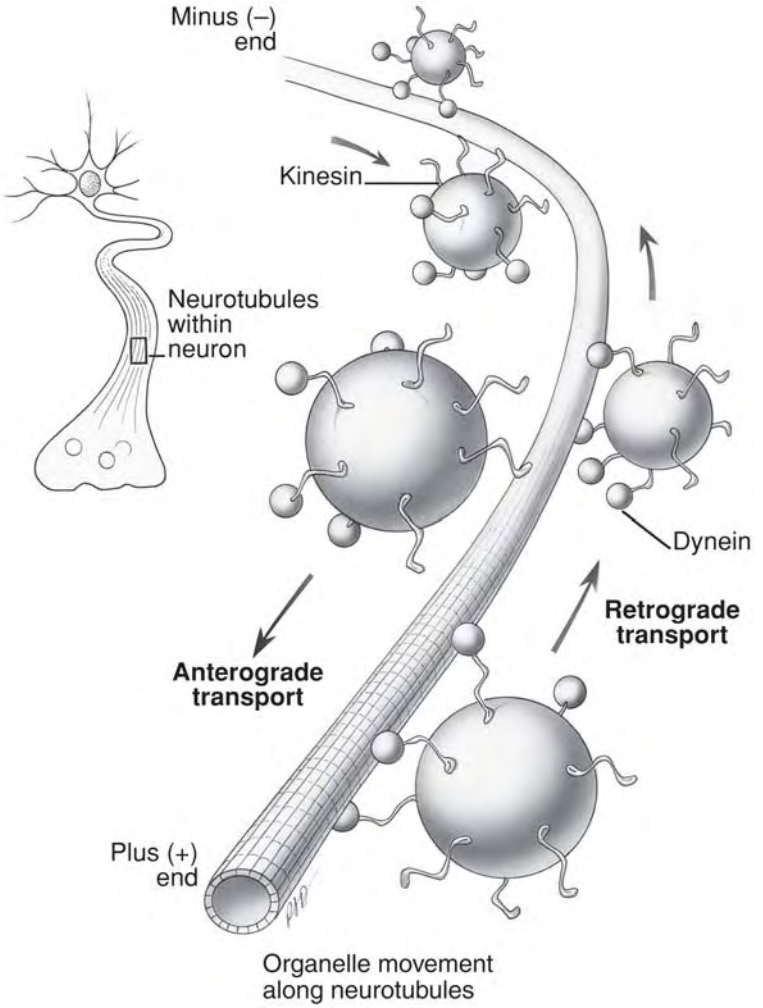


Figure 2.6: Schema illustrating the anterograde and retrograde transport of synaptic vesicles and other organelles along neurotubules. After their components are synthesized within the endoplasmic reticulum and GA, the *organelles* are assembled within the cell body. While in the cell body, the organelles bind with the motor proteins *kinesin* and *dynein*. Kinesin has the means to power their rapid movement via fast axonal anterograde transport to the *plus* (+) end of each neurotubule toward the nerve terminals. The motor is presumed to be transported back to the cell body in an inactive form. The organelle-bound kinesin molecules interact transiently with the microtubule during the anterograde transport via the neurotubule. The retrograde motor protein dynein is transported to the terminal in an inactive form, becomes activated, binds to degraded membranes and organelles, and then is conveyed by retrograde transport to the *minus* (–) end of the microtubules toward the cell body for disposal. Kinesin appears to have a fan-shaped tail that binds to the organelle to be moved and two globular heads that bind to the neurotubule. A hingelike site is present midway along the kinesin molecule. The similarities between kinesin and myosin of muscle suggest that the movement is produced by the sliding of kinesin molecules along the tracks of the neurotubules. Neurons have adapted an ancient mechanism of transport, in that kinesin and dynein are present in single-celled organisms and eukaryotic cells.

per day. There is both anterograde and retrograde fast transport, but only anterograde slow transport. The anterograde fast transport conveys mitochondria and the precursors of smooth endoplasmic reticulum, synaptic vesicles, and plasma membrane. The fast retrograde system includes conveying of such structures as mitochondria, "multivesiculate" bodies (can be degradative structures), and vesicles containing such ligands as nerve growth factors (*see* "Neurotropic Factors and Tropic Factors") taken up by receptor-mediated endocytosis. Mitochondria travel in both, or either, the anterograde and retrograde direction. The neurotubules in association with certain *force-generating motor proteins* (neurotubule-based motors) act as intracellular molecular engines for fast transport, also called *neurotubule-dependent transport*. This fast transport is generated by the molecular motor proteins *kinesin* and *dynein* that are linked with ATP (**Fig. 2.6**). They are responsible for generating the forces for the organelle movements that underlie neurotubular axonal transport. ATP is obligatory, as it furnishes the energy for the fast transport in either direction. These proteins and ATP seem to provide a mechanistic basis for microtubules-associated movement.

The following is a current scheme describing the role of these molecular motor (motility) proteins in fast transport (**Fig. 2.6**). Both anterograde motor kinesin and retrograde dynein attach to appropriate binding sites on the precursors or organelle to be transported. The organelle is conveyed by anterograde transport along the "rail" of the track on the neurotubule by the "molecular motors" of kinesin and is powered by ATP on the organelle toward the plus (+) or axon terminal end of the neurotubule. During this phase, the dynein is transported in an inactive form. The kinesin is then transported back in an inactive form to the cell body for recycling. The retrograde motor dynein, after being transported in an inactive form to the terminal, is activated and becomes the motor to organelles that are destined to be transported along the rails of the track on the neurotubules toward their minus (–) or cell body ends. Each neurotubule contains several tracks along which different particles move. On a single neurotubule, (1) a vesicle can pass another vesicle moving in the same direction on a separate track or (2) two vesicles can move bidirectionally in opposite directions simultaneously on separate tracks. In addition, a vesicle can shift from one to another tubule.

The slow axonal transport is anterograde and involved with the movement of soluble enzymes and the components of the cytoskeleton and plasma membrane. Proteins and other substances are conveyed to renew and maintain the axoplasm of mature neurons and to supply the axoplasm for axon and dendrite growth of developing and regenerating neurons. The protein dynamin has been suggested to be the motor protein with a role in slow transport.

Conceptually, axonal transport is an expression of the unity of the neuron in that, through transport, a continuous communication is maintained between the cell body and its processes. By this means, the cell body is kept informed of the metabolic needs and condition of its most distal parts. Through axonal uptake of extracellular substances, such as nerve growth factor followed by retrograde transport, the cell body can sample the extracellular environment. However, retrograde transport has its debit side, in that through this mechanism, neurotropic viruses such as rabies, herpes simplex, and poliomyelitis are conveyed to the central nervous system. Defects in microtubules might be involved in some human neurologic disorders.

Dendrites, Axons, and Presynaptic Terminals

Dendrites contain the same cytoplasmic organelles (e.g., Nissl bodies and mitochondria) as the cell body of which they are true extensions. The axon is specialized for transmission of coded information as all-or-none action potentials. The axon arises from the *axon hillock* of the cell body at a site called the *initial segment* and extends for a distance of less than 1 mm to as much as 1 m before arborizing into *terminal branches* (**Figs. 2.1 and 2.5**). The axon hillock, initial segment, and the axon lack Nissl bodies. The branches of an

axon could have two types of *bouton*. Each branch ends as a *terminal bouton* (bouton terminaux or end-foot) that forms a synapse with the dendrite, cell body, or axon of another neuron. In addition, along some branches, there are thickenings called *boutons en passage,* which form synapses with another neuron or smooth muscle fiber. The dendrites of many neurons are studded with tiny protuberances called *spines* (e.g., pyramidal neurons of the cerebral cortex; *see* **Figs. 25.1** and **25.2**). These dendritic spines increase the surface area of the membrane of the receptive segment of the neuron. Located on them are over 90% of all the excitatory synapses in the central nervous system (CNS). Because of their widespread occurrence on neurons of the cortical areas of the cerebrum, they are thought to be involved in learning and memory (Chap. 25). The term *neuropil* applies to a dense tangle of axons, dendrites, synapses, and neuroglia within the CNS, which is seen in gray matter, notably in the cerebral cortex.

Synapse

The *synapse* is the site of contact of one neuron with another (**Fig. 2.1**). A submicroscopic space, the synaptic cleft, which is about 200 Å, exists between the bouton of one neuron and the cell body of another neuron *(axosomatic synapse)*, between a bouton and a dendrite *(axodendritic synapse)*, and between a bouton and an axon *(axoaxonic synapse)*. In addition, *dendrodendritic synapses* (between two dendrites) have been noted (e.g., in the olfactory bulb and retina). The axon of one neuron might terminate in only a few synapses or up to many thousands of synapses. The dendrite–cell body complex might receive synaptic contacts from many different neurons (up to well over 15,000 synapses). The termination of a nerve fiber in a muscle cell (neuromuscular junction) or a glandular cell (neuroglandular junction) is basically similar to the synapse between two neurons. The synapse of each axon terminal of a motoneuron on a voluntary muscle cell is called a *motor end plate* (**Figs. 2.1, 2.5, 8.1,** and **8.2**).

The cell membrane of the axon at the synapse is the *presynaptic membrane*, and the cell membrane of dendrite-cell body complex, muscle, or glandular cell is the *postsynaptic membrane*. The *subsynaptic membrane* is that region of the postsynaptic membrane that is juxtaposed against the presynaptic membrane at the synapse. A concentration of mitochondria and *presynaptic vesicles* is present in the cytoplasm of the bouton; none are present in the cytoplasm adjacent to the subsynaptic membrane. Most neurons contain at least two distinct types of vesicle: (1) small vesicles 50 nm in diameter and (2) large vesicles from 70 to 200 nm in diameter. The vesicles contain the precursors of the active neurotransmitter agents (Chaps. 3 and 15).

NEUROTROPHIC FACTORS AND TROPIC FACTORS

Trophism refers to the ability of certain molecules, called trophic (nutritional) factors, to promote cell survival. Neurotrophic factors are polypeptides that support survival, growth, regeneration, and plasticity of neurons. Most types of neuron are generated in excessive numbers, followed later by the death of "surplus" cells soon after axons reach the vicinity of their target (*see* Apoptosis, Chap. 6). This type of neuronal cell death is regarded to be a consequence of the competition for the limited amount of neurotrophic factors released by target cells (e, g., embryonic muscle cells). This is an adaptive means of adjusting the number of neurons of each type to the number of target cells to be innervated. The "trophic effect" exerted on neurons is illustrated by the trophic influences of "taste nerve fibers" upon the taste buds (Chap. 14). Not only do the gustatory nerve fibers convey taste information, but they also have critical roles in both the maintenance and regeneration of taste buds. Following transection of the gustatory nerve fibers, the taste buds degenerate. In time, if and when the transected fibers regenerate into the oral epithelium, new functional taste buds will differenti-

ate from epithelial cells, Presumably, only taste fibers elaborate the essential trophic factors to induce the formation of new taste buds from the oral epithelium. Trophic activity could occur at any time from embryonic life through adulthood. Although a progressive reduction in activity occurs with age, it is never completely lost. To many neurobiologists, the terms *growth factor* and *trophic factor* are synonymous.

In addition to trophic effects, there are *tropic effects*. Tropism refers to the ability of certain molecules to promote or to guide the outgrowth and directional growth or extension of neuronal processes (axons and dendrites) (Chap. 6).

Neurotrophins are a class among many neurotrophic factors that have important roles in the survival of neurons and have widespread effects throughout the CNS and peripheral nervous system (PNS). Neurotrophins include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3), and neurotrophin 4/5 (NT 4/5). Examples of related trophic factors include fibroblast growth factor (FGF), the epidermal growth factor family (EGF) and cytokines. The cytokines (e.g., interleukin, a leukemia-inhibitory factor) are extracellular or membrane-anchored polypeptides that mediate communication between cells via cell surface receptors.

Trophic factors, as indicated, have roles in promoting the successive stages in the cycle of neuronal differentiation, growth, survival, and programmed cell death (*see* Apoptosis, Chap. 6). In addition, neuronal cells respond selectively to trophic factors. For example, all olfactory receptor neurons (ORNs) have a short life-span of 4–6 weeks (Chap. 14) during which they are regulated by trophic factors. They are continually being replaced throughout life. Evidence indicates that the expression of genes encodes the polypeptide trophic factors to regulate the generation and differentiation of precursor olfactory neuroepithelial cells to become mature ORNs and then to be replaced following apoptosis (Chap. 14).

Nerve growth factor is the prototypical neurotrophic factor. NGF was characterized by Levi-Montalcini and Cohen, who were awarded the 1986 Nobel Prize. NGF is a polypeptide with a defining role in the survival and maturation of neurons of the sensory (dorsal root) ganglia and of ganglia of the autonomic nervous system, both derivatives of the neural crest (Chap. 6). NGF is also a trophic factor for such CNS cholinergic neurons as those of the basal forebrain that project to the hippocampus. NGF is derived from the cells of an appropriate target tissue at the correct time during development and is capable of maintaining the viability of the innervated neurons. This is substantiated by the demonstration that an injection of antibodies to NGF into newborn mice results in total degeneration of sympathetic ganglia. NGF of the target tissue is internalized into the appropriate neuron following binding with specialized high-affinity membrane protein receptors (transmembrane receptor tyrosine kinases) located on axon terminals. The molecules of NGF are conveyed by retrograde transport to the cell body. Presumably, the resulting signal transduction involves the expression of proto-oncogenes that act to promote neuronal survival. When the axoplasmic transport to the cell body is disrupted, the neuron degenerates despite the release of NGF by the target tissue.

Considerable interest currently is being directed to the possible therapeutic uses of neurotrophic factors. They could have roles in slowing, preventing, and even reversing the course of such neurodegenerative afflictions such as Alzheimer's disease (*see* AD, Chap. 25), amyotrophic lateral sclerosis (*see* ALS, Chap. 12), Huntington's disease (Chap. 24), and Parkinson's disease (Chap. 24). Because different cell types respond selectively to individual growth factors, these factors could become important in the treatment of these conditions.

STRUCTURE OF PERIPHERAL NERVES AND GANGLIA

Peripheral nerves include both cranial and spinal nerves. Peripheral ganglia are collections

of cell bodies associated with the peripheral nerves. Each nerve consists of three basic tissue elements: (1) axons, (2) Schwann cells (neurolemma) and myelin sheaths (interstitial element), and (3) endoneurium, perineurium, and epineurium (connective tissue component). A peripheral ganglion consists of the same three elements: (1) neuronal cell bodies and axons, (2) inner satellite cells (interstitial element), and (3) outer satellite cells (connective tissue element).

A peripheral nerve with its numerous nerve fibers is comparable to a telephone cable. The axons are analogous to the wires and the Schwann cells and the endoneurium to the insulation encapsulating each wire. Groups of insulated nerve fibers are bound together into fascicles by the perineurium. In turn, groups of fascicles are bound together by the epineurium. Each of these layers is continuous with its counterpart in most peripheral ganglia. The connective tissue elements contain the blood vessels that nourish the neurons; they are also essential for the strength and flexibility exhibited by nerves. The flattened cells of the perineurium form a sheath that acts as a physiological barrier preventing substances from reaching the fascicles of axons. This is a means of maintaining an optimal environment for axonal activity. The numerous generally longitudinally organized collagen fibers are so oriented as to resist the stretching of axons. Impulse conduction is altered in slightly stretched axons.

The myelin sheath, which surrounds an axon, is a structure composed of many continuous spiral laminated layers of the plasma membrane resembling the layers of a jelly roll (**Fig. 2.7**). Schwann cells form the sheath In the PNS, whereas in the CNS, it is elaborated by oligodendroglia (**Fig. 2.10**).

The myelin sheath is interrupted at regular intervals by *nodes of Ranvier* (**Figs. 2.1, 2.5,** and **2.7**). The interval between adjacent nodes is an internode. Each internode is ensheathed by one Schwann cell. The length of an internode is roughly proportional to the diameter of the fiber together with its myelin sheath; the thicker the fiber, the longer its internode. In addition, the diameter of a fiber and the length

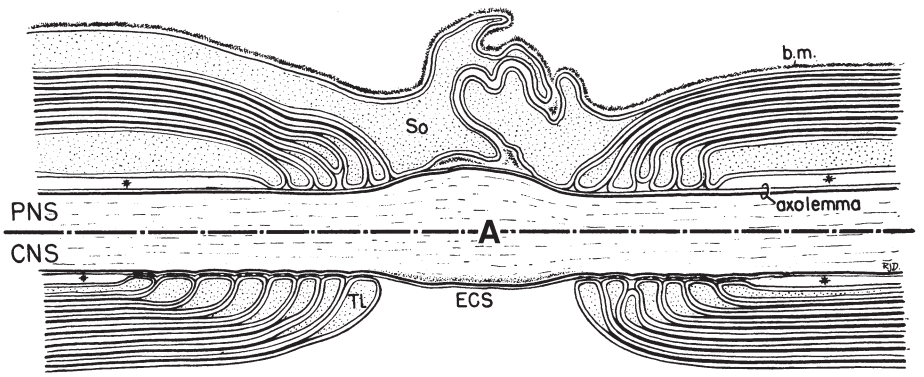


Figure 2.7: Regions of the nodes of Ranvier in the peripheral nervous system (PNS) compared with those in the central nervous system (CNS). In the PNS, the Schwann (neurolemma) cell has an outer collar (So) of cytoplasm, which loosely interdigitates in the nodal region with the outer collar of the adjacent Schwann cell. In the CNS, the axis cylinder (A) in the nodal region is exposed directly with the extracellular space (ECS). In both the PNS and CN,S the compact-layered myelin surrounding the axis cylinder forms terminal loops (T.L.), which are in close apposition to the axolemma; this apposition might form a "seal" preventing ready movement of materials between the periaxonal space (∗) and the nodal region. The Schwann cell is covered by a basement lamina (b.m.). (Courtesy of Dr. R.P. Bunge and the American Physiological Society.)

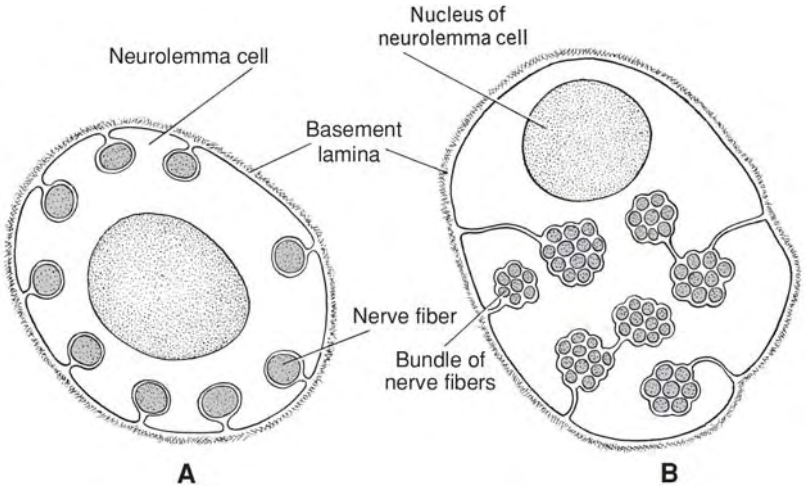


Figure 2.8: Unmyelinated fibers of the peripheral nervous system. **(A)** Nine unmyelinated fibers enclosed in individual troughs of a Schwann (neurolemma) cell. **(B)** Clusters of groups of fine fibers enclosed in troughs of neurolemma cells in the olfactory nerve. (After Bunge, 1994.)

of an internode are directly related to the speed of conduction of the nerve impulse: *The greater the diameter of a fiber, the faster the speed of conduction*. Three features of the nodes are important: (1) Nerve fibers branch at a node, (2) a high concentration of mitochondria in the axis cylinder at these sites indicates a local high level of metabolic activity, and (3) extracellular fluids are close to the axis cylinder at each node. Nerve fibers are bound together in fascicles by connective tissue. Nearly all nerve fibers over 2 μm in diameter are myelinated and those under 2 μm are unmyelinated.

Adjacent to the outer surface of each Schwann cell is a basal lamina, which is synthesized by the Schwann cells. It is a homogeneous layer composed of such proteins as type IV collagen and laminin. The glial cells and neurons of the CNS are not associated with a basal lamina. This layer could have a critical role in the regeneration of peripheral nerve fibers (*see* "Regeneration in the Peripheral Nervous System").

Whereas a myelinated nerve fiber is ensheathed in its private layer of Schwann cells, a group of as many as 20 or more *unmyelinated fibers* might share a common Schwann cell (**Fig. 2.8**). The unmyelinated fibers are separated from one another; each is embedded in a private trough of the surface of a Schwann cell's plasma membrane. The axons of the olfactory nerve present an unusual arrangement. Up to two dozen or more axons are grouped into clusters of several fine fibers enclosed in the same trough of a Schwann cell.

NEUROGLIA (GLIA)

Neuroglia (glia) are the supportive cells that surround the cell bodies, dendrites, and axons of neurons in both the CNS and PNS. In mammals, glia outnumber neurons by 10–50 times depending on the region of the CNS. They constitute about one-half of the total volume of the human brain. Neuroglia (nerve glue) were originally considered to have relatively passive and limited roles within the CNS, but now are known to function at high rates of metabolic activity. During development, neuroglia guide migrating neuronal precursors from the neuroepithelium to their destinations, where patterns of neuronal circuitry are formed (Chap.

6). Throughout life, they are important in the maintenance and sustenance of neurons and their circuits and the release of trophic factors.

Classification of Glial Cells

Like neurons, glial cells defy a rigid classification. Those of the CNS include *astrocytes* (astroglia), *oligodendrocytes (*oligodendroglia*), microglia, and ependymal cells.* The astroglia and oligodendroglia are called *macroglia* (**Fig. 2.10**). The "glial" cells of the PNS consist of *Schwann cells* that surround nerve fibers and *perineuronal satellite cells* surrounding the cell body. These cell types, now considered to be functionally indistinguishable, are collectively called *neurolemma cells*. All of these cells except microglia are derived from ectoderm (Chap. 6). The Schwann cells and satellite cells originate from the neural crests derived from ectoderm. Microglia are mainly of mesodermal origin. Glial cells can divide mitotically throughout life in contrast to neurons, which do not. In the CNS, the neurons and glial cells are separated from each other by an extracellular fluid in the 10- to 20-nm-wide intercellular space (**Fig. 5.6**) comprising 15–20% of the brain's volume. The glial cells have no synapses, do not generate action potentials, and presumably are not directly involved in information processing.

Multiple Roles of Glia

The following are some of the essential roles in which glial cells are actively involved: (1) Glia provide the organized scaffolds that give the CNS structural support for neurons and their circuitry (Chap. 6). (2) Certain glial cells (radial glia) are critical in guiding the developing neurons during migration from their sites of origin to their correct destination and in directing the paths for the outgrowth of their axons. (3) Glial cells produce growth and trophic factors that are key elements in CNS regeneration and plasticity. (4) Oligodendrocytes and Schwann cells produce myelin sheaths. (5) Microglia function (a) as scavengers removing debris produced following injury or neuronal death and (b) in the immune surveillance of the CNS. (6) Astrocytes are important for maintaining homeostasis of the microenvironment of the extracellular fluid for neuronal function by buffering the pH and regulating the potassium ion concentrations. They act as bridges that shuttle nutrients from the capillaries to the neurons (**Fig. 2.9**). (7) Glial cells are involved in the production of cerebrospinal fluid (CSF) and of extracellular fluids that coat, support and protect neurons (Chap. 5). (8) Glia proliferate to form astrocytic scars to repair nervous tissue following injury (reactive gliosis).

Astrocytes

Astroglia constitute a heterogeneous morphologic and functional population occupying the spaces surrounding each CNS neuron. There are *protoplasmic astrocytes* in the gray matter and *fibrous astrocytes* in white matter. Others include Bergmann cells in the cerebellum, Muller's cells in the retina, pinealocytes in the pineal gland, and pituicytes located in the posterior lobe of the pituitary gland. These cells contain 8- to 10-nm-wide microfilaments composed of polymerized strands of *glia fibrillary acetic protein* (*GFAP)*, a specific biochemical marker for astrocytes that can be revealed through immunohistochemistry. Thus, astroglia can be distinguished from neurons for diagnostic purposes.

The cell bodies and processes of astrocytes are interconnected by gap junctions to form a matrix in which the *neurons* are embedded and separated from each other. In addition, astrocytes can act synergistically as a *functional syncytium,* allowing for the interchange of ions and molecules between the astrocytes and the extracellular fluids.

Both glial cells and neurons have negative membrane potentials, indicating that their cell membranes are permeable to potassium ions. Because their cell membranes have only a few potassium channels, astrocytes do not generate action potentials (Chap. 3). Each astrocyte could have several processes that extend among the neurons before terminating in different places as expansions called *end-feet* (**Fig. 2.9**) that (1) form a jacket in contact with the basement membrane of a capillary, (2) are juxta-

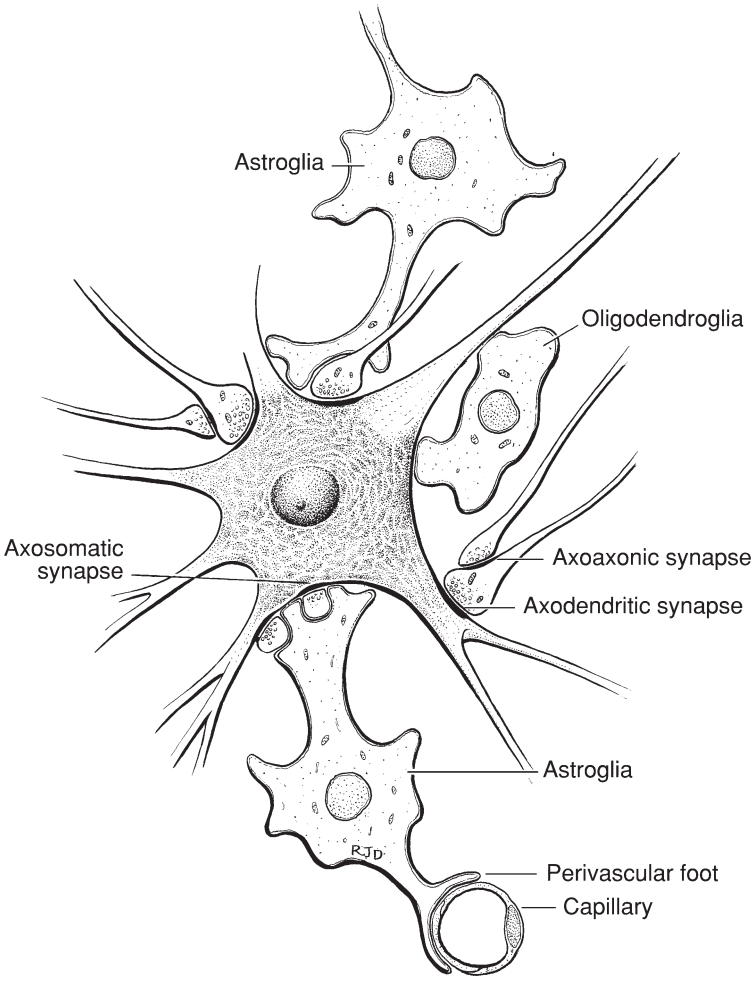


Figure 2.9: Relation of a neuron, astroglia, oligodendroglia, and nerve terminals. Note axosomatic synapse, axodendritic synapse, and axoaxonic synapse. Astroglia have processes extending to a capillary and to neurons.

posed with the free surfaces of the cell bodies and dendrites and envelop the synapses, thereby insulating synapses from each other, (3) come into contact with the pia mater of the pial-glial limiting membrane adjacent to the subarachnoid space, and (4) make contact with ependymal cells of the ventricular system (**Fig. 5.5**). Astrocytes store and transfer metabolites such as glucose from the capillaries to the neurons, and they take up excess potassium from the extracellular potassium sinks via potassium channels. Additionally, following intense neuronal activity, they take up glutamate and neurotoxins that accumulate in the extracellular spaces and synaptic clefts. Following the uptake of excess potassium ions from focal high-concentration *sinks,* the astrocytes can then transfer the excess ions via their gap junctions to regions within the astrocytic syncytium, where the potassium ion concentration is lower (known as spatial buffering). This prevents the spreading depression that results from

the presence of high extracellular concentrations of potassium ions that can trigger excessive neuronal depolarization (Chap. 3). In essence, astrocytes have roles in regulating and maintaining the homeostatic composition of the extracellular fluid (ionic microenvironment and pH) essential to the normal functioning of the neurons of the CNS. The ability of these cells to divide throughout life could explain, in part, why tumors of astrocytic origin are the most common CNS tumors. Astrocytes might secrete such neurotrophins as NGF and BDNF, which are important in promoting the survival of some neurons.

Oligodendrocytes

These CNS cells are the equivalents of Schwann cells of the PNS (**Figs. 2.1** and **2.10**). They are the cells that make and maintain CNS myelin. There are two types of oligodendroglia: *perineuronal satellite cells,* which are closely associated with cell bodies and dendrites in the gray matter, and (2) *interfascicular cells*, which are involved in myelination of axons in white matter. The numerous processes of Individual oligodendrocytes form the myelinated internodes for as many as 70 axons. As noted earlier for peripheral nerve axons, the myelin sheath is a continuous layering of spiral lamellae of the oligodendroglial plasma membrane (**Fig. 2.10**). Myelination of many axons commences prenatally. Most pathways in the human brain are not fully myelinated until 2 years after birth. Oligodendrocytes can participate in the remyelination that can occur following acute or chronic demyelination. This so-called *spontaneous remyelination* takes place in such diseases as multiple sclerosis and could explain the clinical improvement observed in different demyelinating diseases.

Microglia

Microglia exist as (1) *resting microglial cells* in normal CNS (called *resident brain macrophages*), which can become converted into (2) *activated* or *reactive* nonphagocytic microglia capable of producing cytokines that become (3) *phagocytic* microglia (macrophages). Other sources of macrophages are monocytes (its precursor cell in the blood) and meningial and perivascular cells of CNS blood vessels. They become scavengers after being activated by foreign bodies, brain injury, degradation products, or inflammation and thus function as phagocytes to remove debris from the CNS. The resident microglia are small cells that comprise from 5% to 10 % of all glial cells. They contain lysosomes and vesicles characteristic of macrophages, only sparse ER, and a few cytoskeletal fibers. They are found in the CNS as parenchymal microglia, in the choroid plexus, and in the circumventricular organs (Chap. 21). Microglia could participate in shaping of neuronal circuits by actively eliminating "extra" axon collateral branches without affecting the viability of the neuron itself.

Microglia are the representatives of the immune system, with activated microglia having a key role in immune processing in the CNS. They are the cornerstones for the interaction between the domains of the CNS (neurological) and the peripheral immune system (non-neurological). Microglia join astrocytes in responding to immune factors and are associated with the synthesis of growth factors and adhesion molecules. They can produce and secrete cytokines—the soluble proteins associated with the magnitude of the inflammatory and immune response. Glia can participate in autoimmune disease process by being able to act as antigen-presenting cells and, thus, they serve in the immune surveillance of the CNS. In brief, microglia are dynamic immunocompetent cells that function as vigilant ever-present guardians protecting the vital and vulnerable brain and spinal cord. Microglia can be imaged in vivo by *positron-emitting tomography (PET)* as a means of evaluating microglial activation following a stroke in humans. In this procedure, PET scanning images benzodiazepine receptors of the activated microglia.

Ependyma

The ependymal cells are simple cuboidal glial cells that line the central canal of the spinal cord and the ventricles of the brain,

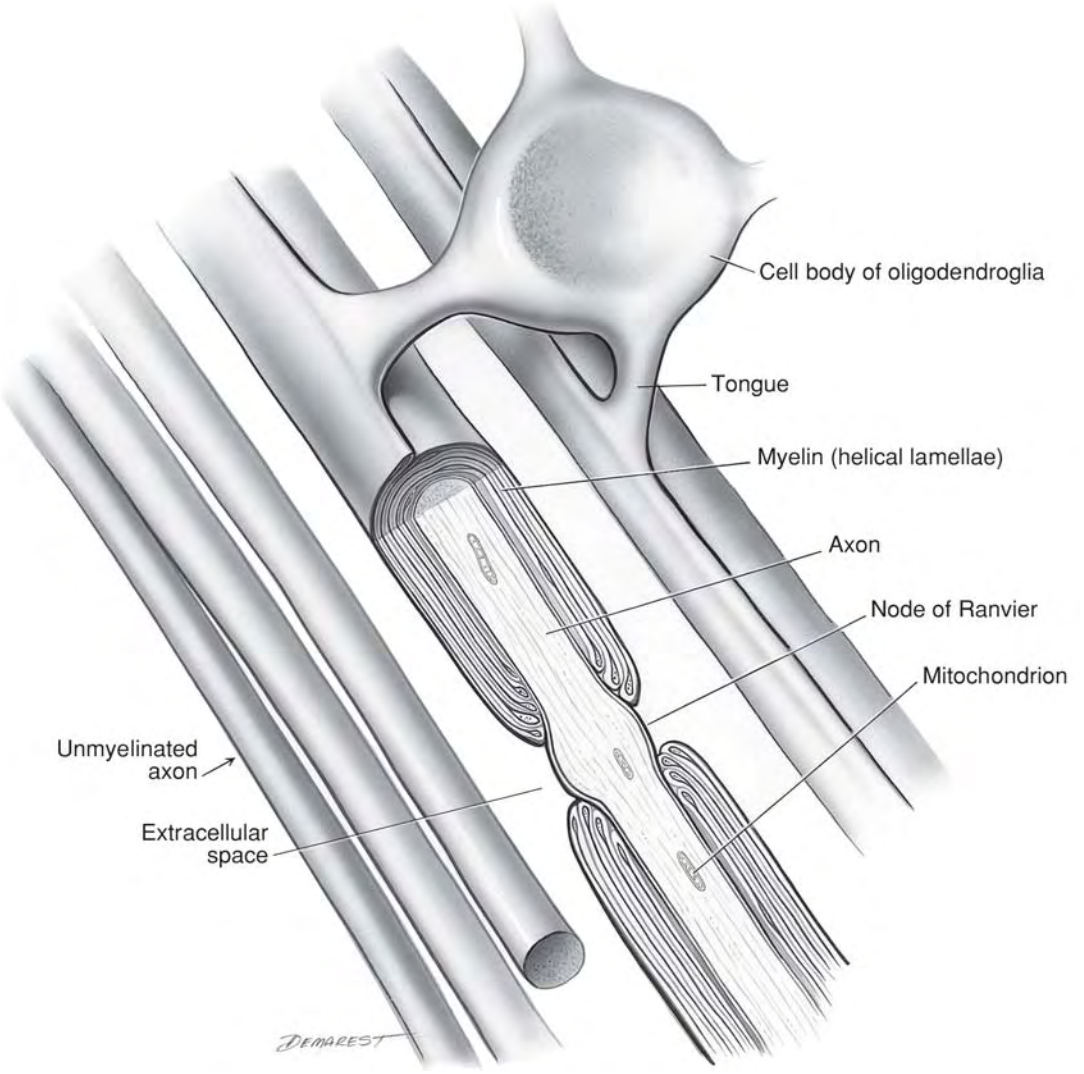


Figure 2.10: Relation of oligodendroglia to the axons of the CNS, as reconstructed from electron micrographs. The three unmyelinated axons on the left are naked. The two myelinated axons of the right share one oligodendroglia cell. The myelin sheaths of each of the myelinated fibers are continuous through the protoplasmic tongue with the glial cell body. The glial tongue spreads out as a ridge, which extends throughout the entire length of an internode. The loop of the cell membrane at the ridge makes the site where the membrane is doubled (myelin unit of two plasma cell membranes) and is continuous as a laminated myelin sheath. (Adapted from Bunge, Bunge, and Ris, 1961.)

including a layer of the tela choroidea. They are involved in the production of cerebrospinal fluid (CSF, Chap. 5). These cells are ciliated in the embryonic stages of humans. The ependymal cells and the adjacent astrocyte end-feet comprise a brain–CFS interface The cellular elements of this interface along with that of the pial–glial membrane on the surface of the brain and spinal cord permit (are not barriers) the exchange of substances between the CSF and

the CNS (Chap. 5). In the floor of the third ventricle are patches of specialized ependymal cells called *tanycytes (*elongated cell) with basal processes that extend through the neuropil to terminate with end-feet on blood vessels and neurons. They have a role in transporting substances between the ventricles and blood. One suggestion is that they transport molecules from the CSF to hypothalamic neurons involved with the regulation of gonadotropic hormone release from the pituitary gland.

Schwann Cells and Satellite Cells

Schwann cells of peripheral nerves and perineuronal satellite cells of sensory and autonomic ganglia in the PNS are the equivalent of the three types of CNS supportive cell (astroglia, oligodendroglia, and microglia). Except for differences in location, Schwann cells and satellite cells are indistinguishable from each other and, hence, are collectively called *neurolemma cells.* Like *astroglia, neurolemma cells* both (1) enclose and separate unmyelinated nerve fibers from each other (**Fig. 2.8**) and (2) are located in the interneuronal space between neurons. Like *oligodendroglia,* they produce myelin sheaths around axons and a few cell bodies of ganglia. Like *microglia, Schwann cells* can become phagocytes in response to nerve injury and inflammation. Unlike glial cells, the Schwann cells secrete collagen, laminin, and fibronectin (extracellular adhesive proteins). These proteins are the main constituents of the *basal lamina* and *extraneuronal matrix* and also of the *basement lamina* that surrounds the cell membrane of axons. The *Schwann cells* invest the peripheral neurons and, thus, are effective in isolating their immediate environment from the extraneuronal space of about 20 μm intercalated between a Schwann cell and a neuron.

PARANEURONS

Paraneurons are cells that, although not usually classified as neurons, possess several features associated with neurons. Some paraneurons are cells with neurosecretory roles. In response to stimuli acting upon receptors within the cell membrane, the paraneuron releases "neurosecretions" from synapticlike granules or vesicles. Many are identical with or related to neurotransmitters. Some are called "sensory" or "receptor cells because a receptor role is dominant (e.g., hair cells of the inner ear, Chap. 16). Others are called "endocrine cells" when the secretory function is primary (e.g., enterochromaffine cells of the enteroendocrine system of the gut, Chap. 20). Examples of paraneurons include the following: (1) *rods and cones* of the retina. Each has a photoreceptive outer segment that is actually a modified cilium. (2) *Olfactory receptor cells* (neurons of the olfactory nerve) of the nasal mucosa. In contrast to all other neurons, these chemoreceptive cells are unique in that they continuously regenerate throughout life from the basal cells of the olfactory mucosa (Chap. 14). (3) Neuroepithelial *taste (gustatory) receptor cells.* These chemoreceptors are innervated by afferent taste fibers of cranial nerves VII, IX, and X (Chap. 14). (4) *Hair cells* of the cochlea, semicircular canals, utricle, and saccule (Chap. 16). The cochleovestibular nerve innervates these ciliated mechanoreceptors. (5) *Merkel cells* of the basal cells of the epidermis (Chap. 10). These mechanoreceptors are innervated by general somatic afferent nerve fibers. (6) *Chief cells* of the *carotid body,* which act as chemoreceptors monitoring the oxygen, carbon dioxide, and pH levels of the blood. (Chap. 14). (7) *Enterochromaffine cells* of the enteroendocrine system (enteric nervous system, Chaps. 15 and 20). These are the source of a variety of gut hormones and neuropeptides, including gastrin, secretin, cholecystokinin, somatostatin, substance P, and vasoactive intestinal peptide (VIP).

NERVE REGENERATION

Axon Reaction

Axonal injury acts as a potent stimulus that sets in motion a series of events directed to preserve a neuron and regenerate its processes (**Fig. 2.11**). This response, known as the axon

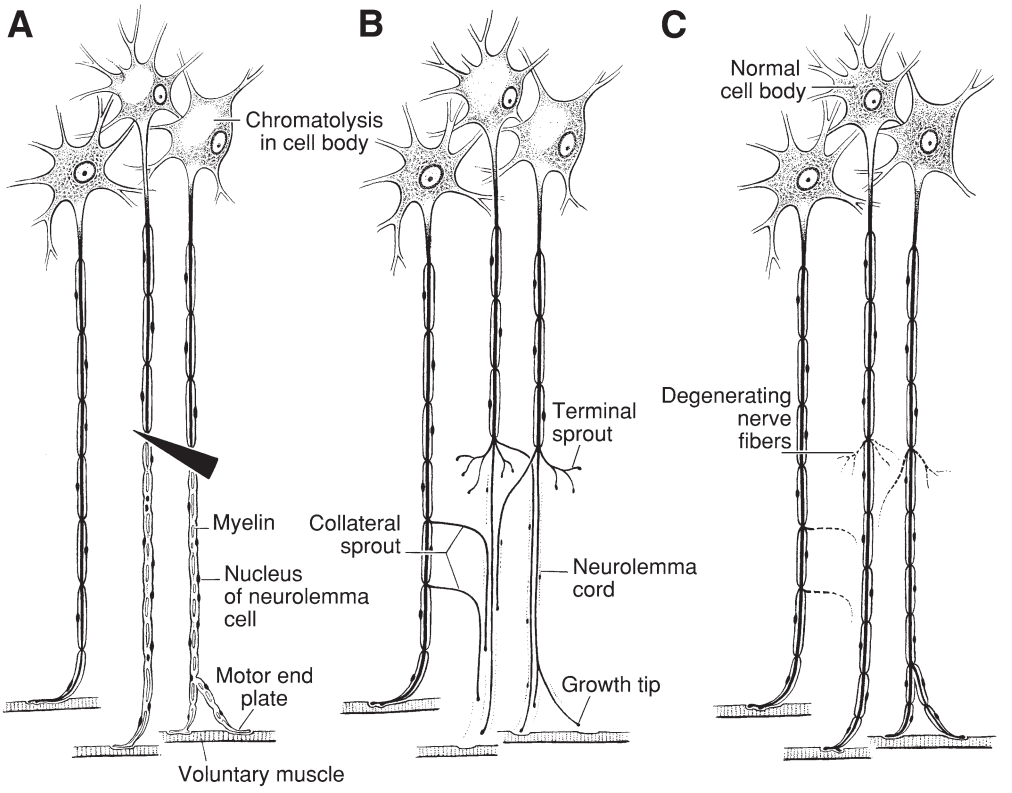


Figure 2.11: Degeneration and regeneration of peripheral somatic motor nerve fibers. **(A)** Several days after transection (at the wedge). Note the central chromatolysis and eccentric nuclei, increase in number of neurolemma cells, and fragmentation of myelin sheaths. **(B)** Several weeks later, the neurolemma cord receives regenerating axis cylinders from the transected fibers and collateral branches from the adjacent normal fiber. **(C)** Several months later, collateral branches of axis cylinders that failed to innervate motor end plates degenerate. The regenerated portions of the fibers contain more internodes than before: hence, they conduct nerve impulses more slowly.

reaction, mobilizes a neuron's cell body, including the nucleus, its axon both proximal and distal to the trauma, and the surrounding neurolemma, and applies to all neurons in the nervous system. The axon reaction is initiated by the release of injury signals, mainly axoplasmic proteins that are activated at the injury site and transported retrogradely to the cell body. With few exceptions, following serious injury, axons located wholly within the brain and spinal cord do not regenerate.

The axon reaction encompasses the expressions of transcription and translation that occur after the cell body of an injured neuron is stimulated by an axoplasmic pathway activated by factors released in the vicinity of the injury site probably derived from the damaged cell membrane and associated neurolemma. This pathway has two phases: (1) retrograde axonal transport of *DNA transcription factors* (molecular "signals") to the cell body followed by (2) import into its nucleus for translation (Sung, Povelones, and Ambron, 2001). These factors affect the transfer of information from DNA molecules to RNA molecules. The transformation (translation) of information from RNA occurs within ribosomes to create the polypeptides essential for regeneration.

The molecular injury signals are of two types: (1) "positive signals" and (2) "negative signals." Positive signals are the axoplasmic factors associated with growth and survival. Some "positive signals" are intrinsic to the axoplasm and others are derived from the glial and neurolemma cells at the site of injury. Such a signal can activate a kinase cascade that initiates and coordinates the essential biosynthetic machinery. The "negative signals" originate from target tissues. This implies the existence of convergent pathways for the activation of the protein synthesis machinery of the cell body. Proteins synthesized in the cell body are conveyed via anterograde axonal transport to the site of trauma. In a sense, the successful regeneration of nerve fibers seen in the mature PNS recapitulates the differentiation and growth of *neurites* during early development (neurite is the generic term that refers to a nerve process when it is not possible to distinguish axon from dendrite, as during embryogenesis (Chap. 6). As a concept, mammalian PNS neurites retain some embryonic "wanderlust" throughout life, as they regenerate in a microenvironment containing growth factor that nurtures and guides their growth in the virtual absence of inhibitory growth factors (Chap. 6). During developmental stages, the local neural environment of the CNS contains an optimal number of "positive molecular signals" to enhance neurite growth. In contrast, the mature CNS generates a number of "inhibitory molecular signals" that limit regenerative neurite growth.

During the axon reaction, the cell body swells and the nucleus becomes eccentrically located. There is an increase and a redistribution of the ribosomes (RNA). They concentrate near the plasma membrane, resulting in a lack of staining in the central part of the soma, known as *central chromatolysis*. This is indicative of an enhanced synthesis of proteins prior to their distribution via axonal transport to the regenerating axons. The severed end of the axis cylinder proximal to the transection is sealed within a day by newly formed plasma membrane just prior to differentiating into a growth cone (Chap. 6). During the weeks following the trauma, the myelin sheaths and axis cylinders of the axons in the distal stumps break up. The fragmented products are ultimately phagocytized by macrophages and removed. At this juncture, events in the PNS and CNS differ.

NERVE REGENERATION

Regeneration in the Peripheral Nervous System (Fig. 2.11)

Following the severance of an axon (axotomy), the evoked axon reaction is expressed by the cell membrane sealing each cut end followed by formation of a growth cone from which filopodial sprouts extend into the narrow gap between the two stumps. The Schwann cells in the proximal and distal stumps divide mitotically to form a scaffold of neurolemma cords (also called perineurial tubes) that bridge the gap. Each cord is surrounded by a basal lamina containing various neurotrophic factors and extends distally to the location of the original nerve terminal. This applies to both myelinated and unmyelinated fibers.

Growth cones grow randomly into the gap by a combination of chemoattraction of the growth cones to neurotropic factors and of the sprouts following contact with a neurolemma cell of a cord (contact guidance). The growth cones contain *actin, a* structural and contractile protein. Each axon elongates and eases forward by contact, like an inchworm. Neurotubules (microtubules), built of the protein *tubulin* that stiffens the trailing axon, develop just behind. Later, the axon is infiltrated with neurofilaments that act as a permanent rigid cytoskeleton. The cords of neurolemma cells upregulate the synthesis of many neurotrophic factors that are secreted and diffuse toward the growing axons. These factors have roles in specific axonal guidance and target finding. The neurolemma cells could even carry a "molecular memory" of whether they had previously ensheathed a sensory, motor, or autonomic axis cylinder. In addition, neurolemma cells provide membrane proteins that aid axonal growth. The sprouts of each axis cylinder can enter several

different cords and, in turn, each cord can receive and act as a guide for the growth cones of the sprouts of several different axons. In a crush site, it is likely that each regenerating axon extends into and remains within its parent cord. Each branch elongates in a cleft between the basal lamina and the neurolemma cells at a rate of 1–3 mm/day. Remyelination of the regenerating branches by the neurolemma could, occur after several weeks. In a sense, the growth of each axon and its remyelination recapitulates early development. The basal lamina is a critical element because it contains such neurotrophic factors as glycoproteins, laminin, fibronectin and tenacin. These factors, especially laminin, are effective substances for the attraction and guidance of axonal outgrowth. Each axon that enters the appropriate cord and then terminates in a suitably matched ending can form a functional connection—motor fibers to reconstituted motor endplates and sensory fibers to reconstituted sensory endings. Axons that do not reach appropriate endings eventually degenerate (**Fig. 2.11**). Nerve cell adhesion molecules such as NCAM (Chap. 6), and neurotrophic factors might have guidance roles during regeneration. The internodal distance between nodes of Ranvier is shorter following regeneration, which accounts for the slower conduction velocities (about 80% of the original) of remyelinated nerves.

A regenerating motoneuron axon might innervate the original synaptic site on a denervated muscle fiber, or at times, a synapse might form at an "ectopic site" on the muscle fiber. The neurolemma cords provide guidance to regenerating axons. Schwann cells guide sprouting axons. Presynaptic myoblasts proliferate and synthesize growth-promoting matrix molecules. Axons might recognize components of the synaptic basal lamina that remained as "basal lamina ghosts" and thus effect selective regeneration to the original synaptic site (Sanes and Lichtman, 1999).

There are a few significant differences between the roles of the neurolemma cells during adult axon regeneration compared to axon elongation in early development. In the adult, the neurolemma cords serve both in trophic (growth) roles and in directive guidance roles for each axon to reach its target (e.g., a muscle to a motor end plate). In early embryonic development, the growth cone of an elongating axon precedes the neurolemma cells to reach and contact the target myotube (embryonic muscle cell) prior to the formation of a motor end plate. In this, the neurolemma cells have a trophic role but not a guidance directive role (Chap. 6)

Collateral Sprouting

A denervated neurolemmal cord exerts trophic influences upon nearby intact nerve fibers, which, in the PNS, respond by sprouting new collateral branches at nodes of Ranvier. This is known as preterminal axonal sprouting or collateral axonal sprouting. The collateral sprout joins the axonless neurolemmal cord and elongates along the cord to form a component of a new motor end plate. Collateral nerve sprouting also occurs in the CNS, but in the latter, neurolemmal cords are absent (**Fig. 2.11**).

Those regenerating axons that do not enter a cord might grow and survive locally to form a neuroma. The resulting tender mass, when irritated, can produce severe pain, called causalgia, which is perceived as coming from the original region supplied by the nerve (*see* Phantom Limb, Chap. 9).

Regeneration in the Central Nervous System

An injury to the brain or spinal cord can be severe and irreversible as a result, in part, of difficulty in regenerating functionally normal axonal connections. About 3 million Americans are victims of traumatic brain injury each year. Over 200,000 (about 10,000 per year) individuals have survived severe spinal injuries, followed by spastic paralysis, sensory loss, and autonomic disturbances. These impairments primarily are attributed to the severed CNS axons being unable to regenerate and re-establish functional synaptic connections. In contrast to the PNS, in the CNS the physical pathway does not remain after an axon is damaged. Instead, the oligodendroglial-lined pathway distal to the injury degenerates and becomes disorganized.

In addition and most importantly, any attempt of an axon to regenerate is blocked by the release of neurotoxic molecular barriers.

During development, both the CNS and PNS contain laminin and fibronectin, proteins that promote neurite growth. Although these proteins are present in the mature PNS, they are virtually absent in the mature CNS.

Experimental evidence shows that the axons of mature CNS neurons possess an innate capacity to regenerate (Ayuago et al., 1991). For example, in rats, segments of peripheral nerve were grafted into the spinal cord, creating a lesion. Many severed CNS axons grew through the graft for considerable distances (Ayuago et al., 1991). Thus, the structural and chemical microenvironment provided by peripheral nerve neurolemma cords supports regrowth in the CNS just as in the PNS. Other experiments designed to suppress CNS proteins produced by oligodendroglia that inhibit regeneration have had some success and suggest that ultimately functional recovery from spinal cord injury might be achievable.

There are a couple of examples in which CNS axons in adult mammals exhibit regeneration. One comprises the neurosecretory hypothalamic neurons that project to the neurohypophysis. Another includes the aminergic and serotonergic fibers projecting from brainstem nuclei that regenerate through the gray matter at the site of a spinal cord injury.

Regeneration Associated With Transection of the Adult Spinal Cord

Many phenomena are associated with neuronal regeneration following trauma involving the transection of the adult spinal cord as expressed in paraplegia (Chap. 12). These include (1) positive events and (2) negative factors associated with the regeneration of the axons, their branches, and synaptic connections. The positive events comprise the recovery of the vascular circulation and the capacity of the injured neurons to express the axon reaction. This is followed by a number of negative factors, which must be recognized and overcome before successful regeneration of the injured axons and the formation of new functional synaptic connections is possible. These factors are expressed in higher vertebrates including mammals and humans.

Positive factors favoring regeneration of neurites include (1) the intrinsic feature of neurons to regenerate branches of neurites, (2) the presence of trophic (growth) promoting factors, and (3) a local environment in which the regenerating sprouts can grow in length. Such conditions are present in the gray matter, where the axon collateral sprouts are observed to regenerate for some distance in the spinal cord (Olson, 1997). Production of antibodies capable of neutralizing myelin-associated neurite-inhibiting proteins and the possibility that stem cells might help facilitate regeneration of axons at the site of a CNS lesion are currently being investigated (Chap. 6).

Negative factors inhibiting the regeneration of neurites include axonal outgrowths that can be blocked by two physical impediments: (1) the development at the lesion sites of glial scars (gliosis by reactive astrocytes and activated microglia) that form impenetrable barriers to the advance of axonal growth cones and (2) the morphologic disorganization of the original structural chain of oligodendroglia in the columns of white matter that deprive the growing axons of guidance routes.

The regenerative response of the axon to the CNS trauma is associated with a change in the molecular factors in the microenvironment of the CNS. Many potent inhibitory or neurotoxic agents are produced or released following the injury that limit or block axonal outgrowth in the CNS of higher vertebrates. Among these are (1) the inhibitory nature of the white matter, which is derived from the membrane proteins of the oligodendroglia and the myelin-associative proteins resulting in the collapse of the axonal growth cones and (2) the secretion of inhibitory neurotoxic molecules into the extracellular matrix (ECM) by reactive astrocytes. This includes upregulation of the powerful inhibitory proteoglycans (modified core protein with highly sulfated oligosaccharide chains) that are components of the ECM. (3) The resultant production of oxygen from free

radicals produces oxidative excess that inhibits neurite growth, as does the release of high levels of glutamate and other inhibitory substances from cells in the injured area, including inflammatory cells such as neutrophils, macrophages, and microglia. Relevant comments on nerve regeneration are noted in the following section and in Chapter 6.

In summary, to enable the regenerating axons of tracts to bridge the gap above and below a spinal cord lesion, three strategies have been adopted. These involve the use among others of neurotrophic factors, various chemical substances, stem cells, and antibodies: (1) application of chemical substances and antibodies that suppress and block the inhibitors (e.g., myelin) of axonal sprouting, growth, and migration; (2) use of neurotrophic factors and chemical substances that stimulate and enhance axonal sprouting, and lengthening of the neuritis; and (3) attempts to devise a method using a chemical substance to form fibrinlike scaffolds within the gap for the guidance of the migrating growth cones to and into the "axonless glial cord" (e.g., like a neurolemma cord in a peripheral nerve) within the spinal cord beyond the gap.

> *The failure of CNS neurons to regenerate their axons after injury is likely to be multifactoral. Injured CNS glia may inhibit regrowing axons and fail to actively provide trophic support to regrowing axons, and injured CNS neurons may fail to receive and respond to their trophic signals. This trophic control problem—deprivation of needed trophic stimuli together with loss of responsiveness to these stimuli—results either in the death of the axotomized neuron or in the failure of the axotomized neuron to reextend. Simultaneous attention to these problems may be essential to the effective promotion of CNS regeneration."* (Goldberg and Barres, 2000).

PLASTICITY AND AXONAL SPROUTING

The neurons of the mammalian CNS possess the capacity to generate new branches (*axonal sprouting*), to form new synapses (*synaptic replacement*), and, thus, to renew neuronal circuits. The expression of this potential, known as *neuronal plasticity* (Chap. 6), is maximal during development, but it is retained in part in the adult CNS. In the mature brain, neuronal plasticity is manifest as a response to such changes as hormonal levels, learning new skills, response to changes in the environment, and injury. This indicates that although the cell body of each neuron is a relatively fixed component within each processing center, the synaptic connections it makes with other neurons are modifiable throughout life. In this respect, the CNS is not a static, "hard-wired" organ but, rather, a sensitive organ capable of limited change induced by natural stimuli. Neuronal plasticity is, in essence, the capability of synaptic connections of a neuron to be replaced, to be increased or decreased in quantity, and to modify functional activity. Presumably, it is influenced by chemical factors such as NGF, the neurotrophin released by the target cells. This plasticity might be involved in part in the functional recovery occurring following small lesions in the brain.

SUGGESTED READINGS

Adamikova L, Straube A, Schulz I, Steinberg G. Calcium signaling is involved in dynein-dependent microtubule organization. *Mol. Biol. Cell*; 2004.

Aguayo AJ, Rasminsky M, Bray GM, et al. Degenerative and regenerative responses of injured neurons in the central nervous system of adult mammals. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 1991;331:337–343.

Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. *Molecular Biology of the Cell.* 4th ed. New York, NY: Garland; 2002

Aldskogius H, Fraher J, eds. *Glial Interfaces in the Nervous System: Role in Repair and Plasticity: International Conference on Glial Interfaces.* Washington, DC: IOS Press; 2002.

Altman J. Microglia emerge from the fog. *Trends Neurosci.* 1994;17:47–49.

Ambron RT, Walters ET. Priming events and retrograde injury signals. A new perspective on the

cellular and molecular biology of nerve regeneration. *Mol. Neurobiol.* 1996;13:61–79.

Ball P. Good little movers: molecular motors. In: *Stories of the Invisible. A Guided Tour of Molecules.* New York, NY: Oxford University Press; 2001;114–137.

Bareyre FM, Schwab ME. Inflammation, degeneration and regeneration in the injured spinal cord: insights from DNA microarrays. *Trends Neurosci.* 2003;26:555–563.

Barres BA, Barde Y. Neuronal and glial cell biology. *Curr. Opin. Neurobiol.* 2000;10:642–648.

Bridgman PC. Myosin-dependent transport in neurons. *J Neurobiol.* 2004;58:164–174.

Bunge MB, Bunge RP, Ris H. Ultrastructural study of remyelination in an experimental lesion in adult cat spinal cord. *J. Biophys. Biochem. Cytol.* 1961;10:67–94.

Bunge RP. The role of the Schwann cell in trophic support and regeneration. *J. Neurol.* 1994; 242:S19-S21.

Cooper G, Hausman R. *The Cell: A Molecular Approach.* 3rd ed. Sunderland, MA: Sinauer Associates; 2003.

Cousin MA, Robinson PJ. The dephosphins: dephosphorylation by calcineurin triggers synaptic vesicle endocytosis. *Trends Neurosci.* 2001; 24:659–665.

Curtis R, DiStefano PS. Neurotropic factors, retrograde axonal transport and cell signalling. *Trends Cell. Biol.* 1994;4:383–386.

De Vellis J, ed. *Neuroglia in the Aging Brain.* Totowa, NJ: Humana Press; 2002.

Dyck PJ, Thomas PK, Griffin JW, Low PA, Poduslo JF, eds. *Peripheral Neuropathy*. 3rd ed. Philadelphia, PA: Saunders; 1993.

Fiala JC, Harris KM. Dendritic structures. In: Stuart G, Sprutson N, Hausser M, eds. *Dendrites.* New York, NY: Oxford University Press; 1999.

Goldberg JL, Barres BA. The relationship between neuronal survival and regeneration. *Annu. Rev. Neurosci.* 2000;23:579–612.

Goldstein LS. The kinesin superfamily: tails of functional redundancy. *Trends Cell Biol.* 1991; 1:93–98.

Haimo LT. Regulation of kinesin-directed movements. *Trends Cell Biol.* 1995;5:165–168.

Harold F. *The Way of the Cell: Molecules, Organisms, and the Order of Life.* New York, NY: Oxford University Press; 2001.

Hol EM, Schwaiger FW, Werner A, Schmitt A, Raivich G, Kreutzberg GW. Regulation of the LIM-type homeobox gene islet-1 during neuronal regeneration. *Neuroscience.* 1999; 88:917–925.

Laming PR, Kimelberg H, Robinson S, Salm A, Hawrylak N, Muller C, et al. Neuronal–glial interactions and behaviour. *Neurosci. Biobehav. Rev.* 2000;24:295–340.

Levi-Montalcini R, Skaper SD, Dal Toso R, Petrelli L, Leon A. Nerve growth factor: from neurotrophin to neurokine. *Trends Neurosci.* 1996; 19:514–520.

Levitan I, Kaczmarek L. *The Neuron: Cell and Molecular Biology.* 3rd ed. New York, NY: Oxford University Press; 2001.

Miller FD, Kaplan DR. Signaling mechanisms underlying dendrite formation. *Curr. Opin. Neurobiol.* 2003;13:391–398.

Murphy S, ed. *Astrocytes: Pharmacology and Function.* San Diego, CA: Academic; 1993.

Murshid A, Presley JF. ER-to-Golgi transport and cytoskeletal interactions in animal cells. *Cell. Mol. Life Sci.* 2004;61:133–145.

Olson L. Regeneration in the adult central nervous system: experimental repair strategies. *Nature Med.* 1997;3:1329–1335.

Ramón y Cajal S. N Swanson, Swanson L (trans). Histology of the nervous system of man and vertebrates. New York, NY: Oxford University Press; 1995.

Rezaie P, Male D. Mesoglia & microglia—a historical review of the concept of mononuclear phagocytes within the central nervous system. *J. Hist. Neurosci.* 2002;11:325–374.

Robinson PJ, Liu JP, Powell KA, Fykse EM, Sudhof TC. Phosphorylation of dynamin I and synaptic-vesicle recycling. *Trends Neurosci.* 1994; 17:348–353.

Sanes JR, Lichtman JW. Development of the vertebrate neuromuscular junction. *Annu. Rev. Neurosci.* 1999;22:389–442.

Satir P. A decade of kinesin, three decades of dynein. *Trends Cell Biol.* 1995;5:266–267.

Schwab ME. Repairing the injured spinal cord. *Science.* 2002;295:1029–1031.

Schwaiger FW, Hager G, Raivich G, Kreutzberg GW. Cellular activation in neuroregeneration. *Prog. Brain. Res.* 1998;117:197–210.

Setou M, Hayasaka T, Yao I. Axonal transport versus dendritic transport. *J. Neurobiol.* 2004; 58:201–206.

Shepherd G. *The Synaptic Organization of the Brain.* 5th ed. New York, NY: Oxford University Press; 2004.

Stuart G, Spruston N, Hausser M, editors. *Dendrites*. New York, NY: Oxford University Press; 1999.

Sung YJ, Povelones M, Ambron RT. RISK–1: a novel MAPK homologue in axoplasm that is activated and retrogradely transported after nerve injury. *J. Neurobiol.* 2001;47:67–79.

Thoenen H, Sendtner M. Neurotrophins: from enthusiastic expectations through sobering experiences to rational therapeutic approaches. *Nature Neurosci.* 2002;5(Suppl):1046–1050.

Tsay D, Yuste R. On the electrical function of dendritic spines. *Trends Neurosci.* 2004;27:77–84.

Vallee RB, Williams JC, Varma D, Barnhart LE. Dynein: an ancient motor protein involved in multiple modes of transport. *J. Neurobiol.* 2004; 58:189–200.

Whitford KL, Dijkhuizen P, Polleux F, Ghosh A. Molecular control of cortical dendrite development. *Annu. Rev. Neurosci.* 2002;25:127–149.

Woolf CJ, Bloechlinger S. Neuroscience. It takes more than two to Nogo. *Science.* 2002; 297:1132–1134.

3
Basic Neurophysiology

Resting Potential
Nernst Equation
Excitability of the Neuron
Graded Potentials and Action Potentials
Structural and Functional Organization of the Neuron
Receptive Segment and Receptor Potentials
Initial Segment and the Integrated Potential
Conductile Segment and Action Potential
Transmissive Segment (Synaptic or Effector Segment)
Synapses and Chemical Transmission in the Central Nervous System
First- and Second-Messenger Systems
Electric (Electronic) Synapses
Neuron as an Integrator
Presynaptic Inhibition and Presynaptic Facilitation
Functional Roles of Dendrites
Some General Concepts Associated With Coding and Neuronal Processing in the Nervous System

Every neuron is said to possess "in miniature the integrative capacity of the entire nervous system." Neurons can transform information and transmit it to other neurons. In most, the dendrite–cell body unit is specialized as a receptor and integrator of synaptic input from other neurons, and the axon is specialized to convey coded information from the dendrite–cell body unit to the synaptic junctions, where transformation functions take place with other neurons or effectors (muscles and glands). To serve these tasks, the neuron is thus organized into (1) a receptive segment (dendrites and cell body), (2) a conductile segment (axon), and (3) an effector segment (synapse) (**Fig. 3.1**).

Prior to describing the connectivity of the nervous system and the way in which neurons interact, important intrinsic physiological and other properties essential to their function will be examined.

RESTING POTENTIAL

The resting neuron is a charged cell that is not conducting a nerve impulse. The plasma membrane, which acts as a thin boundary between the extracellular (interstitial) fluid outside the neuron and the intracellular fluid (neuroplasm) inside the neuron (**Fig. 3.2**), is critical for maintaining this charged state or resting potential. The electric charge across the plasma membrane results form a thin film of positive and negative ions, unequally distributed across the membrane. These are (1) sodium (Na^+) and

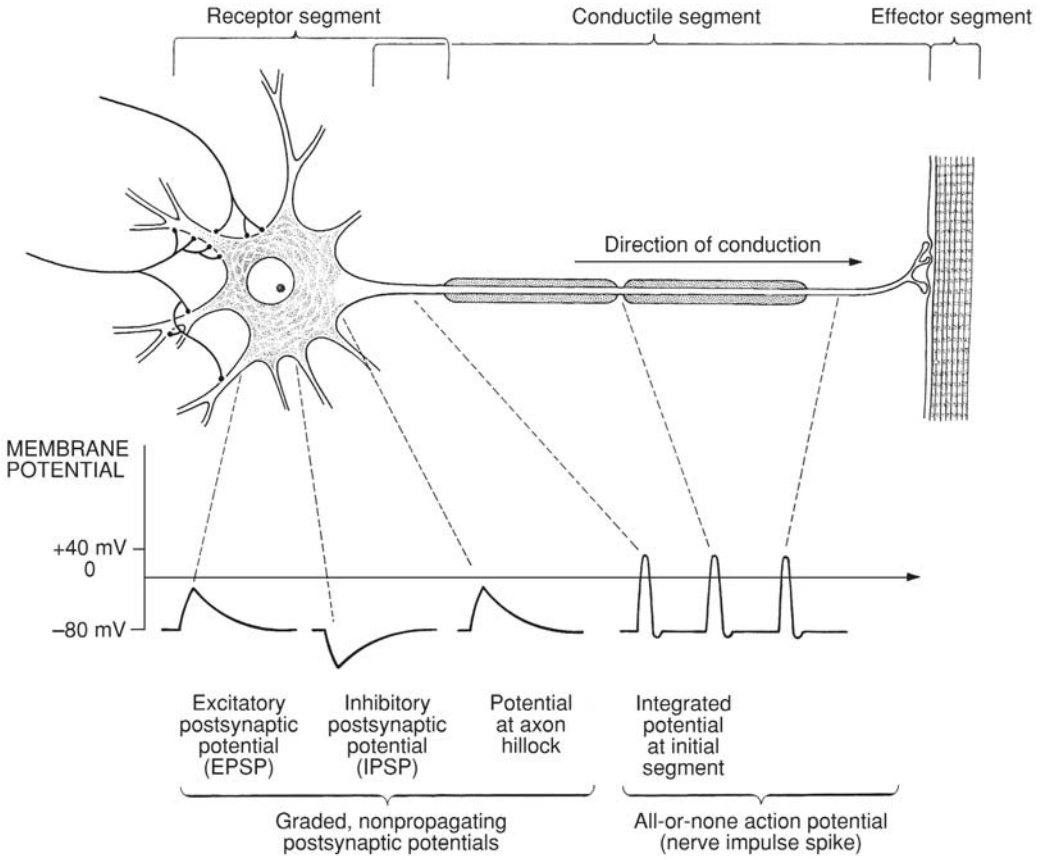


Figure 3.1: Types of electric potential change recorded across the plasma membrane at various sites of a motoneuron. On the surface of the dendrites and cell body are excitatory and inhibitory synapses, which, when stimulated, produce local, graded, nonpropagating potentials. These are exhibited as an excitatory or depolarizing postsynaptic potential (EPSP) and as an inhibitory or hyperpolarizing postsynaptic potential (IPSP). These local potentials are summated at the axon hillock and, if adequate, could trigger an integrated potential at the initial segment and an all-or-none action potential, which is conducted along the axon to the motor end plate. (Adapted from *Gray's Anatomy,* WB Saunders.)

chloride (Cl^-) ions, which are in higher concentration in the interstitial fluid, and (2) potassium (K^+) and protein (organic) ions that are in higher concentration in the neuroplasm. A tendency exists for the Na^+, K^+, and Cl^- ions to diffuse across the membrane from regions of high to low concentration (along concentration gradients), through Na^+, K^+, and Cl^- channels, respectively. The passage of ions across the membrane is known as *conductance*. Thus, the semipermeable plasma membrane is selectively permeable through nongated open channels (Chap. 2) to Na^+, K^+, and Cl^- ions and impermeable to large protein ions. These channels, which are always open, are important in determining the resting potential. The ionic concentrations on either side of the membrane are produced and maintained by a system of membrane pumps (**Fig. 2.4**) called the *sodium* (or *sodium–potassium) pump* requiring metabolic energy released by adenosine triphosphate (ATP). The sodium–potassium exchange pump

is an integral membrane protein that utilizes ATP as an energy source for its role in *active transport*. This transport is an energy-dependent process in which the movement of Na^+ and K^+ ions is "uphill" against a concentration gradient. The activity of the pump results in the passage of three Na^+ ions out of and two K^+ ions into the neuron. This causes the restoration of a concentration of K^+ 30 or more times higher within the neuroplasm than in the interstitial fluid and in a concentration of Na^+ that is 10 times and Cl^- that is 14 times higher in the interstitial fluid than in the neuroplasm. Most neurons do not have a Cl^- pump; hence, Cl^- ions diffuse passively across the membrane. These are the ionic concentrations responsible for establishing an electric potential across the membrane. The transmembrane potential, known as the *resting potential*, is about –60 to –70 mV (millivolts) inside the neuron (**Fig. 3.2**).

The resting potential is in a steady state (*dynamic equilibrium*) requiring metabolic energy to maintain the ionic gradients across the membrane. When the neuron is "at rest," its membrane potential is the result of a balance (involving Na^+ and K^+ ions) between the active fluxes (movements) of ions metabolically driven by *pumps* and the passive fluxes caused by *diffusion*. The active fluxes result from the pump extruding three Na^+ ions for every two K^+ ions it brings into the neuron. The passive fluxes of ions take place through nongated channels. The outward flux of positive charges by the pump tends to hyperpolarize the membrane. The greater the hyperpolarization, the greater the inward electrochemical force driving Na^+ into the neuron and the smaller the force driving K^+ out. The steady state for the neuron is attained when the resting potential is reached at the point when the net passive inward current (movement of electrical charge) through the ion channels exactly counterbalances the active outward current driven by the pump. The steady state is not basically the result of *passive diffusion*, which is the diffusion of a solute down a concentration gradient without the expenditure of energy.

NERNST EQUATION

The *Nernst equation* is fundamental to the nature of electrical potentials of all cells, including neurons. It is derived from basic thermodynamic principles. From this equation, the magnitude of the membrane potential at which ions (e.g., K^+) are in equilibrium across a membrane can be calculated. The Nernst equation is

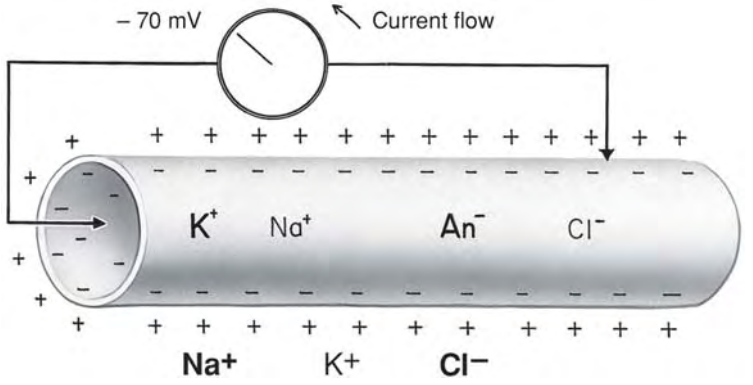


Figure 3.2: Resting potential. The intracellular neuroplasm potential of the normal nerve fiber "at rest" is negative to the extracellular potential. Sodium (Na^+) and chloride (Cl^-) ions are in high concentration in the extracellular fluid, and potassium (K^+) ions and protein (An^-) are in high concentrations in the neuroplasm. The potential across the plasma membrane is –60 to –70 mV.

$$E = 2.3 \frac{RT}{F} \log \frac{C_o}{C_i}$$

where

E = the difference in the electrical potential between inside and outside the neuron, called Nernst potential
R = universal gas constant
T = absolute temperature
F = electric charge per gram equivalent of univalent ions (Faraday's constant)
C_i = concentration of ions inside the membrane
C_o = concentration of ions outside the membrane

The following summary is based on Hodgkin and Huxley's classic studies of the giant squid axon. The resting potential of –70 mV is primarily the result of (1) the much greater concentration of K^+ ions inside than outside the neuron and (2) the passive movement of K^+ ions that diffuse freely through permanently open channels in the membrane. Both of these points have been established experimentally. In addition, only open channels, without gates, are involved in creating resting potentials (gated channels remain closed; see subsequent discussion regarding gates and gating). Thus, the concentrations of ions on either side of the membrane result from the opposite actions of the diffusion forces (flow of K^+ ions out of cell to regions of low concentration) and the electric forces (negative charge on the organic molecules inside the neurons that attract the positive charge of K^+ ions). The diffusion of Na^+ and Cl^- ions contributes only slightly to the resting potential (*see* later). The distribution of the ions is maintained at a steady state by the sodium–potassium pump that drives the Na^+ out of and the K^+ into the neuron. Actually, the pump is a self-regulating system: The more the sodium accumulates inside the neuron, the more active the pump becomes. When the known concentrations of K^+ ions inside and outside the squid giant axon are applied to the Nernst equation, a resting (Nernst) potential of –75 mV is calculated. This predicted figure differs slightly but importantly from the actual resting potential of –70 mV measured by microelectrode studies of the squid axon and is explained by the fact that Cl^- and Na^+ make small contributions. Sodium does not have a major role, because application of the Nernst equation to the known Na^+ concentrations on either side of the membrane yields a potential of +50 mV. The explanation is that Na^+ is kept out of the neuron because there are only a few open sodium channels in the resting membrane. Practically all sodium channels are gated.

The Nernst equation expresses a significant relationship that defines the equilibrium potential inside the cell for the K^+ ion in terms of its concentration on both sides of the plasma membrane. This relation between K^+ concentration and membrane potential is not quite perfect, because, as indicated, Cl^- and Na^+ do make small contributions. A more exact relation is expressed by the *Goldman–Hodgkin–Katz equation*, which takes into account the actual permeability for several ions. On the basis of actual ionic concentrations and ionic permeabilities, calculations using the latter equation agree with the measurements of these values in living cells (see more comprehensive references for detailed accounts).

EXCITABILITY OF THE NEURON

Excitability is a property that enables a neuron to respond to a stimulus and to transmit information in the form of electrical signals. The flow of information within a neuron and between neurons is conveyed by both electrical and chemical signals. The electrical signals, called graded potentials (receptor/generator potentials; synaptic potentials) and action potentials, are all produced by temporary changes in the current flow into and out of the neuron. These changes are deviations away from the normal value of the resting membrane potential. Ion channels within the plasma membrane control the inward and outward current flow. The channels possess three features. They (1) conduct ions across the plasma membrane at rapid rates up to 100,000,000 ions per second, (2) can rec-

ognize specific ions and be selective as to which can pass through, and (3) selectively open and close in response to specific electrical, chemical, and mechanical stimuli. Each neuron is presumed to have over 20 different types of channel with thousands of copies of each channel. The flux (movement of ions) through the ion channels is passive, requiring no expenditure of metabolic energy. The direction of the flux is determined by the electrochemical driving force across the plasma membrane.

The primary role of ion channels in neurons is to mediate rapid signaling. These channels, called *gated channels*, have a molecular "cap" or *gate*, which opens briefly to permit an ion species to pass (**Fig. 3.3**). *Ligand-gated channels* open when a neurotransmitter binds to them; *voltage-gated channels* open and close in response to changes in membrane potential; *modality-gated channels* are activated by specific modalities (e.g., touch, pressure, or stretch). Gating is the process by which a channel is opened or closed during activity. Each channel consists of several plasma membrane-spanning polypeptide subunits (proteins) arranged around a central pore. Each of these classes of channel belongs to a different gene family. Each member of a family shares common structural and biochemical features, which presumably have evolved from a common ancestral gene of that family. The channels of the voltage-gated gene family are selective for Na^+, K^+, and Ca^{2+} ions. The channels for the transmitter-gated channels respond to acetylcholine, gamma amino butyric acid (GABA), and glycine. In the future, other families will be identified when the genes for other ion channels have been sequenced.

Most gated-channels are closed with the membrane at rest. They open when activated following the binding of a ligand (ligand gating), a change in the membrane potential (voltage gating), or the stretch of the membrane (modality gating). In the transmitter-gated channel, the transmitter binds to a specific site on the external face of a channel that activates it to open briefly.

The energy to open the channels is derived (1) from the binding of the transmitter to the receptor protein in the ligand-gated channels, (2) from the changes in the membrane voltage in the voltage-gated channels, and (3) presumably from the mechanical forces resulting from cytoskeletal interaction at the modality-gated channels.

There are two types of membrane response; it could (1) *hyperpolarize* or (2) *depolarize*. During *hyperpolarization*, the membrane becomes more negative on the inside with respect to its outside (i.e., could go from –70 mV to –80 mV; **Fig. 3.1**). During *depolarization,* the membrane becomes less negative inside with respect to its outside and even might reverse polarity with its inside becoming positive with respect to the outside (**Figs. 3.1, 3.4,** and **3.5**); this is still called depolarization because the membrane potential becomes less negative than the resting potential (e.g., from –70 mV to 0 to +40 mV; **Fig. 3.1**).

GRADED POTENTIALS AND ACTION POTENTIALS

Neurons are specialized to generate electrical signals, which are used to encode and convey information. These signals are expressed by alterations in the resting membrane potential. Voltage changes that are restricted to at or near the sites where neurons are stimulated are called *graded potentials.* These can lead to the production of *action potentials (nerve impulses or spikes),* which transmit information for substantial distances along an axon. Two forms of graded potential are *generator (receptor potentials)* and *synaptic potentials*. Generator potentials are evoked by sensory stimuli from the environment (both inside and outside the body). Information that passes from one neuron to another at synapses produces *synaptic potentials* in the postsynaptic neuron. The activity of either generator or synaptic potentials can elicit action potentials, which, in turn, produce synaptic potentials in the next neuron. Synaptic potentials elicited in effectors (skeletal muscle and glands) at synapses can result in the contraction of the muscle or emission of secretory

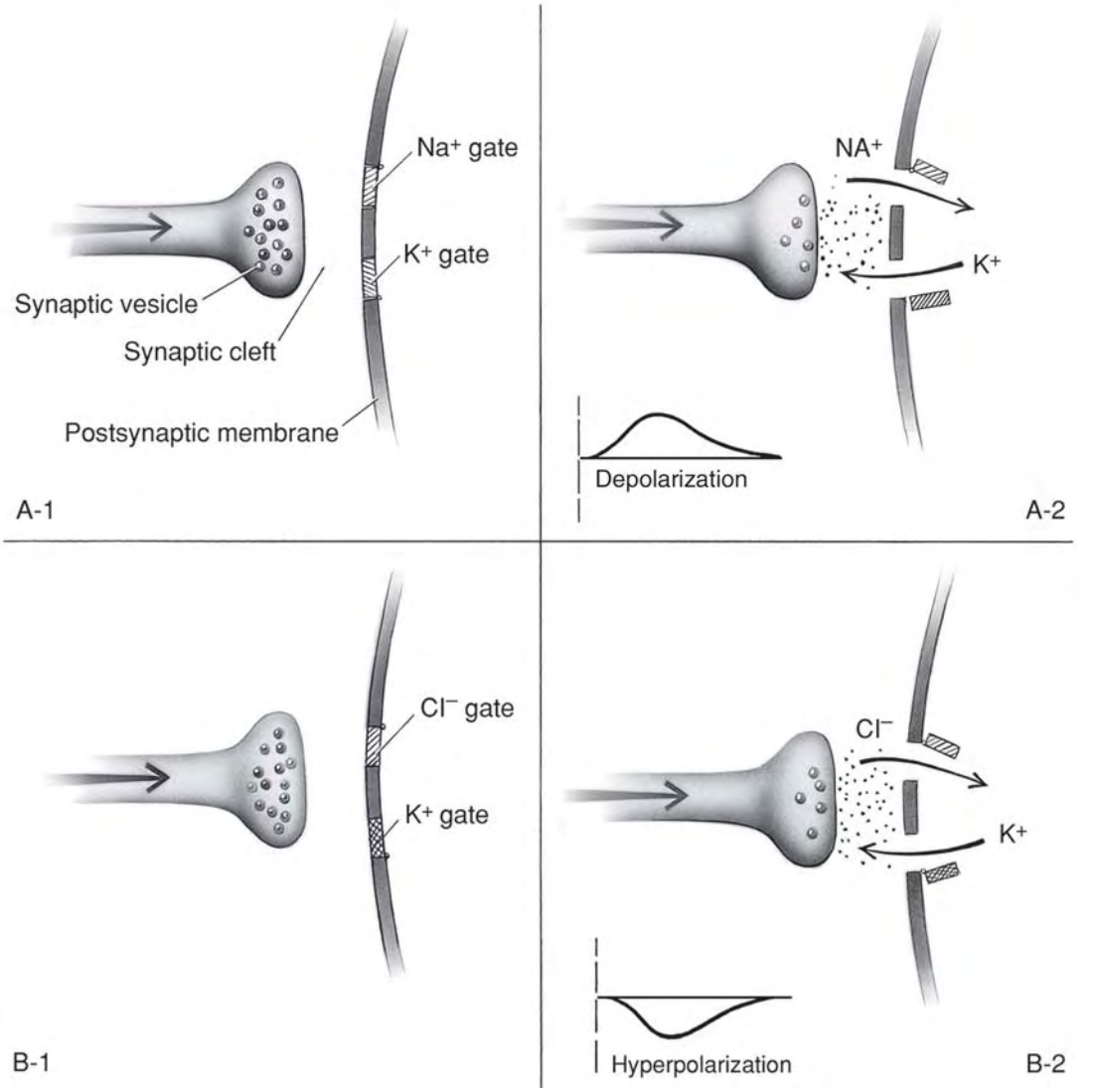


Figure 3.3: Excitatory synapses **(A)** and inhibitory synapses **(B)**. *A-1* and *B-1*, Synapses prior to release of neurotransmitter. *A-2*: Excitatory postsynaptic response (EPSP) following release of neurotransmitter with Na^+ ion inrush through Na^+ gate and K^+ ion outrush through K^+ gate. *B-2*: Inhibitory postsynaptic response (IPSP) following release of neurotransmitter with Cl^- ion inrush through Cl^- gate and K^+ ion outrush through K^+ gate.

product from a gland (*see* "Synapse at Motor End-Plate").

Generator and synaptic potentials differ from action potentials in the way they code information. In essence, graded potentials code information by amplitude modulation (an AM system), and action potentials use frequency modulation (an FM system). The graded potentials code by response amplitude; that is, weak stimuli evoke small potentials (small voltage changes) and strong stimuli evoke large potentials (greater voltage changes), hence *graded responses.* Within the central nervous system (CNS), or at autonomic ganglia, a small depo-

larization (small voltage change), called an *excitatory postsynaptic potential* (*EPSP*), occurs at the postsynaptic membrane of an excitatory synapse; a small hyperpolarization, called an *inhibitory postsynaptic potential* (*IPSP*), occurs at the postsynaptic membrane of an inhibitory synapse (**Fig. 3.5**). The amount of change depends on the strength of the stimulus.

In contrast, action potentials code by response frequency; that is, weak stimuli evoke only a few action potentials per unit time, whereas strong stimuli elicit many action potentials per unit time, but the amplitude of the signal is the same.

The following outline compares graded (generator and synaptic) potentials with action potentials. More details will be discussed later.

Generator and Synaptic Potentials

1. Graded Response: The amplitudes of responses vary in proportion to stimulus intensity—the stronger the stimulus, the larger the change in membrane potential.
2. Maintenance of Response: The membrane potential change could last as long as the stimulus is sustained.
3. Threshold for Response: There is no discrete threshold. Small potential changes could be evoked with the weakest stimulus. For example, one quantum of light or the transmitter from one synaptic vesicle will elicit a weak receptor (rod or cone of retina) or synaptic potential.
4. Summation of Responses: The potentials will sum when the stimuli are presented close together in time or/and space.
5. Response Remains Local: Potentials will spread passively from the stimulus site (site of generation); they are largest at the stimulus site and become progressively smaller away from that site.

Action Potentials

1. All-or-None Response: Regardless of the strength of the stimulus, the potentials are all the same size (about 100 mV or 0.1 V).
2. Transient Response: The potentials are of constant duration (about 1.5 ms).

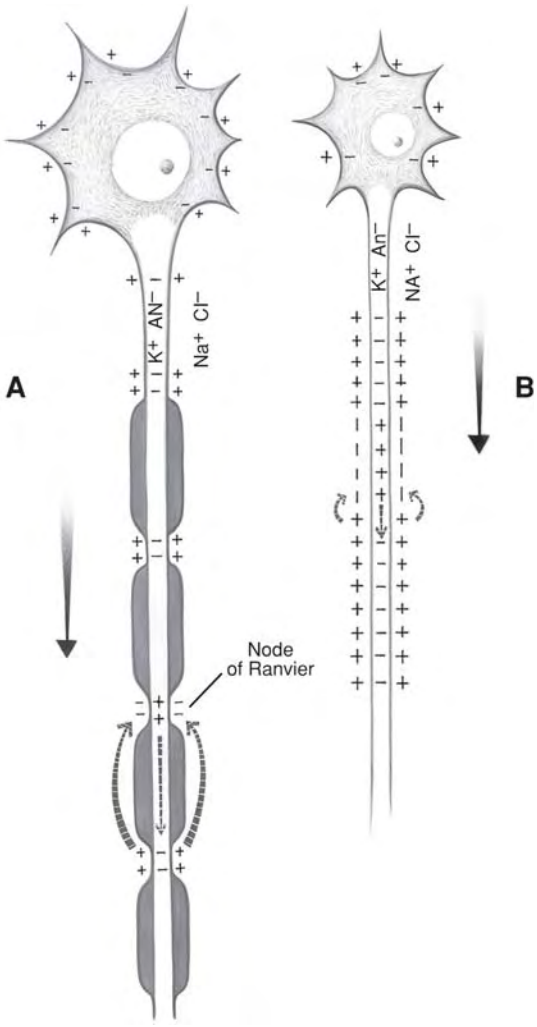


Figure 3.4: A neuron with a myelinated axon **(A)** and a neuron with an unmyelinated axon **(B)** showing the charges on the cell membrane and the location of certain ions in each neuron "at rest" and at active sites (one in each neuron) during conduction of an all-or-none action potential. The minus (–) signs within the neurons signify intraneuronal negativity with respect to the positivity (+) within the extracellular fluid outside the neurons. The two large arrows indicate the direction in which the nerve impulses are propagated. The arrows within the axons indicate the direction of the flow of current. Na^+, sodium; K^+, potassium; Cl^-, chloride; An^- ions, protein.

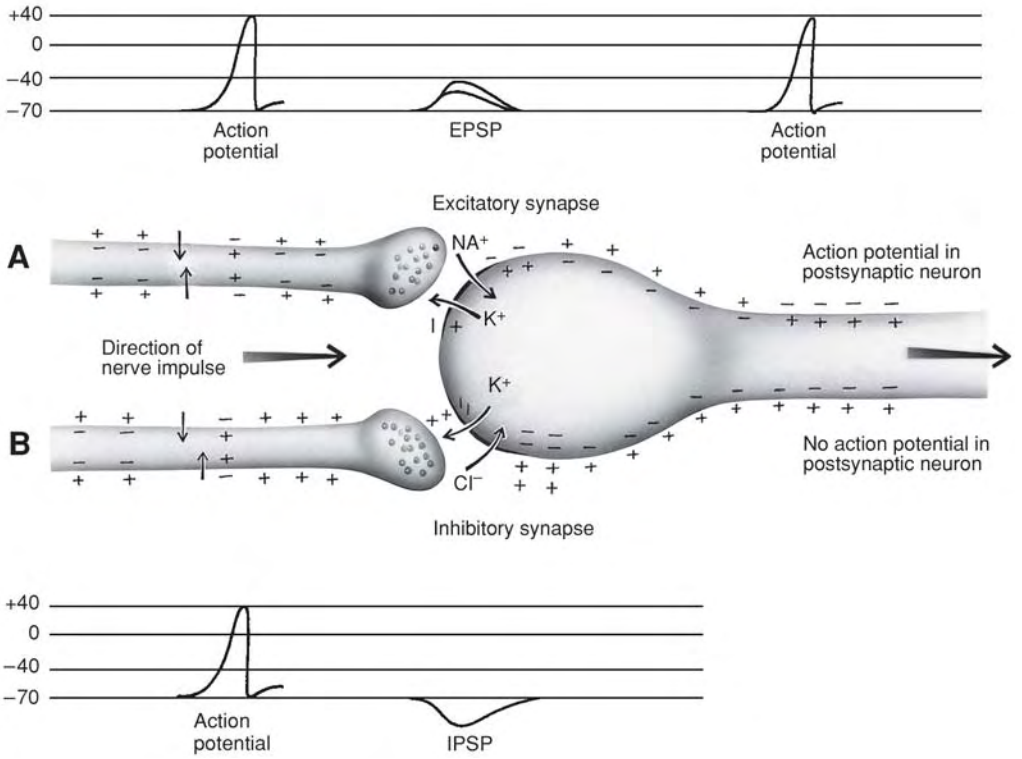


Figure 3.5: Sequences in excitatory **(A)** and inhibitory **(B)** transmission from presynaptic neurons (left) across synapses to postsynaptic neuron (right). **A.** The action potential conducted along the presynaptic axon to an excitatory synapse produces an EPSP, which, in turn, can contribute to the generation of an action potential in the postsynaptic neuron. **B.** The action potential conducted along the presynaptic axon to an inhibitory synapse produces an IPSP, which, in turn, suppresses generation of an action potential in the postsynaptic neuron.

3. Threshold for Response: Action potentials activation requires substantial change in the membrane potential (up to 15 mV).
4. Size Principle: Smaller neurons require less EPSP to reach threshold for an action potential than do large neurons.
5. Refractory Period: An unresponsive period of about 1.5 ms follows every action potential. During this time, another action potential cannot be generated, regardless of the strength of the stimulus.
6. Propagation of Response: Action potentials involve a brief reversal of current limited to only a small area, which is conducted wavelike along its length. An action potential at the beginning of an axon (site of initiation) is of the same strength as at the axon terminal. Thus, the *neural code* for the message conveyed by an axon is based on frequency (number of action potentials per unit time). Additionally, coding is mediated by the pattern (sequencing) of action potentials.

STRUCTURAL AND FUNCTIONAL ORGANIZATION OF THE NEURON

A typical neuron is a cell with (1) a receptive segment, (2) an initial segment, (3) a conductile segment, (4) a transmissive segment, and (5) a trophic segment (**Figs. 3.1** and **3.6**). Each component can be defined by functional criteria.

The *receptive segment* is the portion that senses, receives, and integrates information from numerous synapses for neural processing. It is specialized for the reception of stimuli (input), which results in the generation of local potentials. Each *local potential* generated at a synapse is the product of a transient shift of the membrane potential in the immediate vicinity of the synapse of the receptive segment. The membrane can respond by either hyperpolarizing or depolarizing. This occurs because of local alterations in the permeability to certain ions (i.e., Na^+, K^+, and Cl^-). In those neurons in which the dendrites and cell body comprise the receptive segment, the local potential is called the *synaptic (postsynaptic) potential* or *chemical potential* (*see* Local Potential later). The channels involved in generating these potentials are chemically (transmitter) gated. In sensory neurons of the peripheral nerves, the receptive segment is located in sensory receptors in the body (e.g., touch receptors). This segment contains modality specific gated Na^+ and K^+ channels. In these neurons, the local potential as already indicated, are called the *receptor* or *generator potential*.

The *initial segment* is the *junctional* or *trigger zone* between the receptive zone and

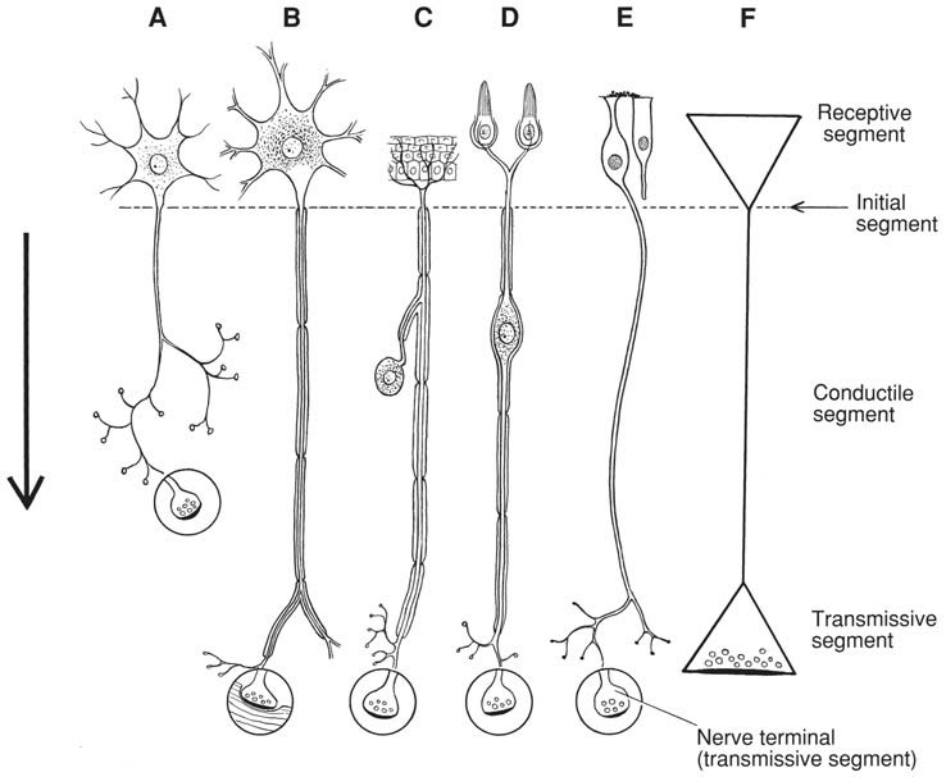


Figure 3.6: Structural and functional organization of representative neurons. Most neurons are composed of a receptive segment, an initial segment, a conductile segment, and a transmissive segment. The transmissive segment of each neuron is encircled. Arrow indicates the normal direction of conduction of the nerve impulse. (A) Interneuron; (B) lower motoneuron; (C) sensory neuron with cell body in cranial or spinal ganglion; (D) neuron of vestibulocochlear nerve; (E) neuron of olfactory nerve; (F) functional organization of neuron. Note that the cell body (trophic segment) could be located within the receptive segment (A, B, and E) or within the conductile segment (C and D). The receptive segment of the vestibulocochlear nerve is associated with a hair cell.

conductile zone. It is the locale where the collective effects of the receptive zone generate an *integrated (integral) potential*, which is able to trigger an *action potential* in the conductile segment (**Fig. 3.1**).

The *conductile segment* is specialized for the conduction of neural information from the receptive segment to the transmissive synaptic segment. To perform this role, the conductile segment conveys all-or-none *action potentials* (nerve impulses). This segment contains voltage-gated Na^+ and K^+ channels.

The *transmissive segment* contains the presynaptic membrane and the synaptic vesicles. The action potentials arriving from the conductile segment activate, through voltage-gated channels, the release of the chemical neurotransmitter, which, in turn, influences the receptor sites of the postsynaptic cell.

The *trophic segment* is the cell body that is the metabolic center essential for the viability of the neuron. In most neurons, the trophic center is usually located within the receptive segment. In sensory neurons of peripheral nerves, the cell body is located within the conductile segment (**Fig. 3.7**).

RECEPTIVE SEGMENT AND RECEPTOR POTENTIALS

In most neurons, the receptive segment consists of the *dendrite–cell body* unit. In the sensory neurons of the peripheral nerves, it is the nerve terminals distal to the first node of Ranvier.

Dendrite–Cell Body Unit

The cell membrane of the dendrite–cell body unit is a postsynaptic membrane, also known as the *receptor membrane*, because its permeability channels are responsive to the *transmitters (neurotransmitters)* released by the presynaptic neuron. Thus, its channels are transmitter gated (chemically gated). In addition, each channel is permeable to both Na^+ and K^+ ions or to both K^+ and Cl^- ions. When stimulated, this membrane propagates a response, called a *receptor potential or synaptic potential*, which is a graded response. Each graded response propagates a potential along the cell membrane for a short distance and lasts for only 1 or 2 ms, but is not sufficient to generate an action potential (**Fig. 3.1**). Successive stimuli, when timed close together, are additive and enhance or facilitate the graded response. When a synaptic potential is increased in size, it is said to be *facilitated*. Action potentials are not generated across the membrane of the dendrites and cell body because these membranes do not contain voltage-sensitive Na^+ and K^+ channels. In contrast, in most neurons, action potentials are generated in the region of the initial segment because of the high concentration of voltage-sensitive Na^+ and K^+ channels in the membrane at this site.

Excitation of the receptor membrane is explained as the response to a transmitter that partially depolarizes the postsynaptic membrane. Such a response is graded and known as an excitatory postsynaptic potential (EPSP) (**Figs. 3.1**, **3.3**, and **3.5**). It, like the action potential noted later, is associated with Na^+ inrush into the segment and K^+ outrush through the same chemically gated channels driven by molecular pumps (**Fig. 3.3**). A single EPSP does not lower the membrane potential sufficiently to generate an action potential (**Fig. 3.5**). However, many EPSPs, generated collectively, can, by facilitation, become strong enough to lower the membrane potential of the initial segment sufficiently to generate an action potential (nerve impulse). The transmitter eliciting EPSPs opens channels that allow both Na^+ and K^+ to cross the plasma membrane.

Whereas an EPSP brings a neuron to a state closer to the level where it is more likely to generate an action potential, an *inhibitory postsynaptic potential (IPSP)* does the opposite. Inhibition is the hyperpolarization of the postsynaptic membrane in response to a transmitter (e.g., –70 mV to –80 mV) (**Fig. 3.1**). The inhibitory response is associated with Cl^- inrush and K^+ outrush through the channels of the postsynaptic membrane (**Figs. 3.3** and **3.5**). The transmitter eliciting IPSPs opens channels

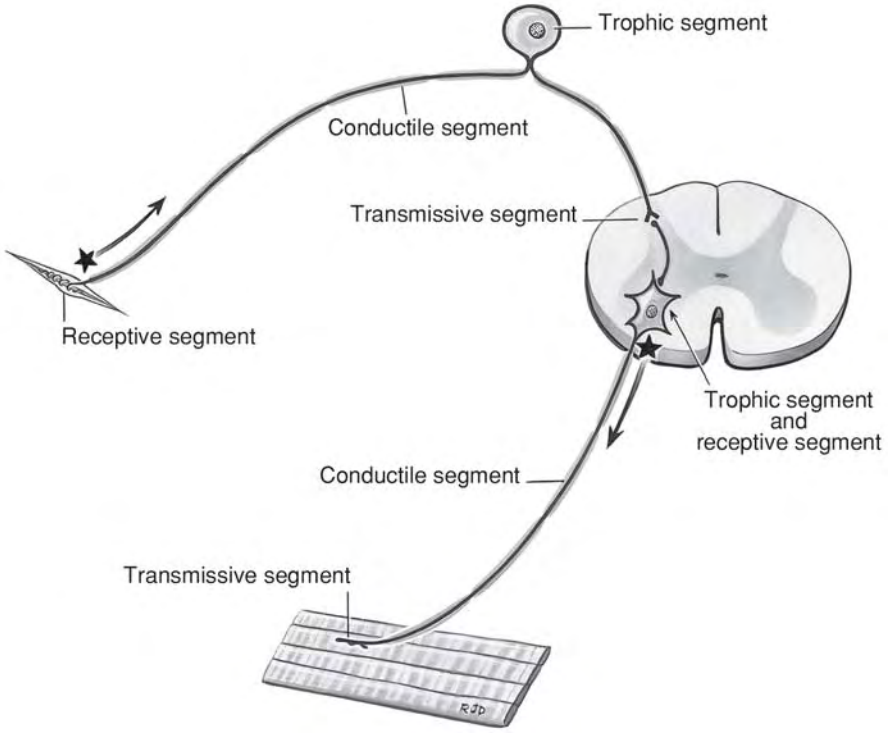


Figure 3.7: A structural and functional schema of a neuron. A neuron can be divided into segments other than the classical dendrite, cell body, axon, and nerve endings. The sensory neuron can be divided as follows: The receptive segment, which conducts with decrement, is the nerve ending; the initial segment (star) is the nodal site where the decremental conduction becomes the nondecremental (all-or-none) conduction of the conductile segment; the conductile segment, which conducts without decrement (all-or-none), extends from the initial segment to the synaptic endings within the spinal cord; the terminal (transmissive) segment includes the synaptic endings. In this neuron, the cell body is located within the conductile segment. The motoneuron can be divided as follows: The receptive segment includes the dendrites and cell body; the initial segment (star) is located just distal to the cell body; the conductile segment goes to the motor end plates; and the terminal segment is located within the motor end plates. In this neuron, the cell body is located within the receptive segment. The cell body is the trophic segment, which is the metabolic center of the neuron.

that allow both Cl^- and K^+ to cross the plasma membrane. The major inhibitory transmitters are GABA and glycine. The postsynaptic receptors for these transmitters are associated with channels permeable to Cl^- ions. The resulting influx of Cl^- ions into the neuron hyperpolarizes the membrane and produce IPSPs.

Excitatory postsynaptic potentials oppose IPSPs. A neuron could have numerous excitatory postsynaptic channels as well as numerous inhibitory postsynaptic transmitter-gated channels. Both types are able to alter the ionic permeability of the receptor membrane. The integration of such synaptic activity is the function of the dendrites and cell body of a neuron (*see* later). In essence, the receptive segment integrates synaptic inputs, which, if they summate sufficient excitatory activity to reach the initial segment, can trigger an action potential in the axon (**Fig. 3.1**).

In general, excitatory synapses, evoking EPSPs, are found in greater numbers in the dendrites, whereas inhibitory synapses are found in greater numbers in the cell body. This is a functionally desirable distribution. The EPSPs can summate to excite the neuron, whereas the IPSPs, by being located closer to the initial segment, can effectively control and modulate the quantity of excitatory influences arriving at the initial segment to trigger an action potential. The nozzle of a hose is analogous to the role of the inhibitory synapses; the set of the nozzle (degree of inhibition) regulates the amount of water (summated EPSPs) ejected by the hose.

Receptive Segment of Peripheral Sensory Neurons

The sensory or afferent neurons conveying information from the external and internal environments via the peripheral nerves to the CNS have a particular structural organization. The peripheral sensory endings of these fibers, many of which are associated with specialized sensory receptors such as the spiral organ of Corti in the inner ear and neuromuscular spindles within muscles, have a short receptive segment (**Fig. 3.6**). The plasma membrane contains modality-specific gated Na^+ and K^+ channels. They produce graded potentials that are called *receptor* or *generator potentials*. Pressure in touch receptors and stretch in muscle spindle sensory endings open these channels. When the generator potentials reach the first node of Ranvier, which is the initial segment, an integrated potential is generated.

INITIAL SEGMENT AND INTEGRATED POTENTIAL

The *initial segment* of an axon of most neurons, or the *first nodal site (node of Ranvier)* of peripheral sensory neurons (**Figs. 3.6** and **3.7**), is a specialized segment where an *integrated potential* is generated. In essence, this is the integrative region where the (algebraic) summation of the EPSPs and IPSPs of the receptive (synaptic) segment are recorded and integrated. It is called the *trigger zone* or *spike-generating zone* because it can trigger or generate the action potential (AP) of the axon. This occurs because for all neurons it is the site of the lowest threshold, roughly –45 mV. When this threshold is reached, the newly generated integrated potential of this segment orchestrates and initiates the spike. The integrated potential will spark the firing of an AP only if the excitation exceeds the inhibition by a critical minimum at the trigger zone. If the membrane potential falls below the spike-firing threshold, no more action potentials are generated.

Each receptor transfers the stimulus energy into the electrochemical energy of the neuron and, thus, establishes a common language for all the sensory systems.

CONDUCTILE SEGMENT AND ACTION POTENTIAL

The *conductile segment* is the part of a neuron specialized to convey an *action potential (AP, nerve impulse)*, which is a rapidly propagated traveling wave of electrical excitation advancing without decrement in an all-or-none fashion along the axon's plasma membrane. Because of the sharp inflection recorded on the oscilloscope, it is also called a *spike* (**Fig. 3.1**). All-or-none refers to the fact that an impulse travels either as a full-blown spike or not at all. The *integrated potential* of the initial segment activates the voltage-gated channels of the conductile segment. This alters the permeability of the cell membrane. When the stimulus to the axon lowers the resting potential to a critical voltage level, usually about 10–15 mV less negative than the resting potential, an explosive event occurs with the opening of the voltage-gated channels of the conductile segment. The result is the AP, which is an expression of the sudden depolarization. This is the result of changes in conductance associated with the opening of the voltage-gated Na^+ and K^+ channels. For a few milliseconds, a polarity reversal occurs from the resting potential of –60 to –70

mV to the AP of +30 mV with an excess of negative charge outside the neuron. The axis cylinder gains Na^+ and loses K^+ ions during the passage of the AP. At each point along the axon, the voltage-gated Na^+ channels are activated first and then followed by the opening of the voltage-gated K^+ channels (**Fig. 3.4**). The conductance of the Na^+ and K^+ ion channels presumably occurs through separate and independent channels. Through these independent channels, the AP is propagated sequentially along the nerve fiber at essentially a constant velocity. As soon as the AP passes by each patch along the nerve fiber, the K^+ conductance is increased by the opening of the voltage-gated K^+ channels and, thus, the cell membrane returns to its resting level. The repolarization of the membrane occurs when the K^+ conductance restores internal negativity.

The following is a rough approximation. The assumptions that the membrane potential (1) is solely the result of K^+ leads to a value near that of the resting potential, and (2) is solely the result of Na^+ leads to a value near that of the action potential. These assumptions are essentially correct because K^+ is primarily responsible for the resting potential and Na^+ is primarily responsible for the action potential.

In summary, the movement of ions across the plasma membrane through voltage-gated channels produces the AP. The movement only occurs after the channels are open, which results in changes in the distribution of charges on either side of the membrane. The influx of Na^+ ions reverses the resting charge distribution. This is followed by an influx of K^+ ions, which repolarizes the membrane by restoring the initial charge distribution.

Unmyelinated Fibers

In an unmyelinated fiber, the AP is propagated sequentially along all parts of the cell membrane of the axon. Each depolarized point on the membrane produces a flow of current (AP) that triggers depolarization of the adjacent point. This continues the length of the axon (**Fig. 3.4B**). The AP travels along the cell membrane as a chain reaction at a constant speed. It regenerates itself from point to point along the axon without loss of amplitude; that is, it propagates via voltage-gated channels without decrement. The smooth progression of the AP is characteristic of unmyelinated fibers.

Myelinated Fibers and Saltatory Conduction

The AP in a myelinated nerve fiber is propagated by discontinuous spread or saltatory (hop or jump) conduction, in which the AP hops along the nerve fiber from node of Ranvier to node of Ranvier (**Fig. 3.4A**). The current spreads only from an active depolarized node to an inactive polarized node by activating its voltage-sensitive Na^+ and K^+ channels. These channels are highly concentrated in the axis cylinders exposed at the nodes. The myelinated internodes act as passive conductors. Myelinated fibers are fast conductors of action potentials. The speed of conduction of the AP is related to the thickness of the myelin sheaths and the length of the internodes of a nerve fiber. The thicker the myelin sheath and the longer the internodes, the faster is the conduction rate. Myelin improves the signaling (conductile) efficiency of an axon.

TRANSMISSIVE SEGMENT (SYNAPTIC OR EFFECTOR SEGMENT)

The *transmissive* or *synaptic segment* is that portion (or portions) of a neuron through which it exerts its influence on another neuron, muscle, or gland cell (**Fig. 3.7**). Anatomically, this is the presynaptic portion of a synapse comprising the presynaptic membrane and vesicles containing neurotransmitters or their precursors. Physiologically, the arrival of an AP in the transmissive segment activates the voltage-gated calcium channels in the presynaptic membrane to trigger the inward passage of Ca^{2+} ions. This is the critical final step for the release of neurotransmitter into the synaptic cleft. These voltage-gated Ca^{2+} channels control what is essentially the secretory function of a neuron, which is, in essence, a secretory cell.

The synapse acts as a one-way valve permitting the action potential of a neuron to exert its

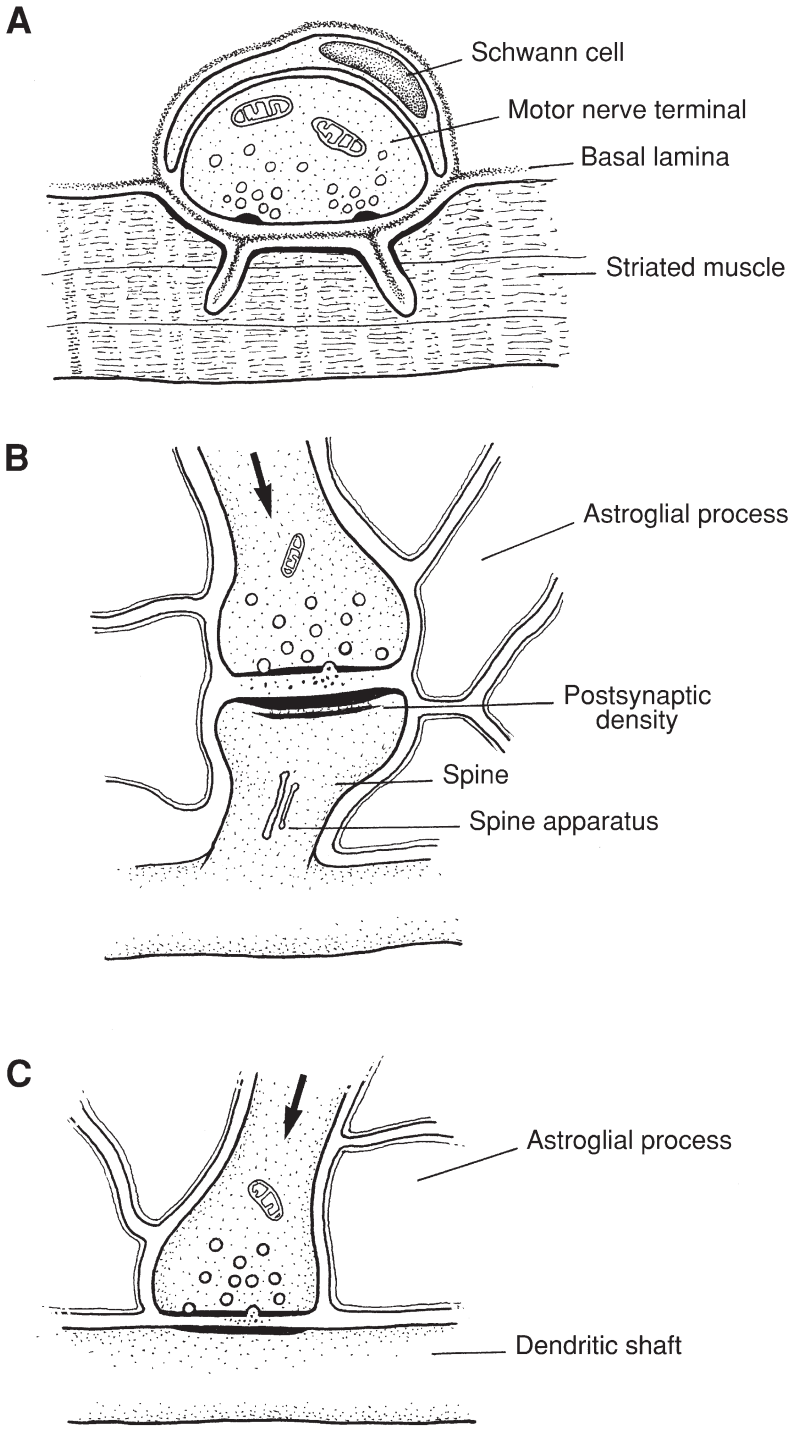
influence through the release of neurotransmitters across the synaptic cleft to the receptive segment of the postsynaptic neuron. An exception is the axoaxonic synapse (**Fig. 2.9**) in which the synapse is between two transmissive segments (discussed later in connection with presynaptic inhibition and excitation).

Synapse at Motor End-Plate (Neuromuscular Junction) (Figs. 3.8 and 3.9)

The synapse at the motor endplate between an axon terminal and voluntary muscle is a well-documented example of interaction at a synapse. Acetylcholine (ACh) is the transmitter at this synapse. The ACh is released into the synaptic cleft from a vesicle as a quantum with each quantum containing about 6000–10,000 ACh molecules. The release is continuous, with a quantum resulting in the slight activity known as miniature end-plate potentials (MEPPs) that do not produce an action potential (AP) in the postsynaptic membrane (sarcolemma of muscle fiber). Each AP impulse releases from 100 to 200 quanta. A more active synaptic transmission commences with the depolarization of the membrane by the arrival of the AP at the presynaptic terminal. Upon depolarization, the voltage-sensitive Ca^{2+} channels open, resulting in an influx of Ca^{2+} ions into the terminal. The Ca^{2+} facilitates the binding and confluence of many synaptic vesicles to the presynaptic membrane. Following the arrival of volleys of APs and the increase in the influx of Ca^{2+} ions into the nerve terminal, there is a 100,000 times surge in ACh molecules as numerous quanta are released by exocytosis into the synaptic cleft. Following exocytosis the vesicle membrane is recycled (**Fig. 3.10**).

The ACh molecules activate an estimated 20–40 million ACh receptor sites on the sarcolemma of a motor end plate. This results in EPPs (end-plate potentials) in the membrane that depolarizes the sarcolemma adjacent to the neuromuscular junction (NMJ). This activates its voltage-sensitive Na^+ and K^+ channels of the sarcolemma to generate APs. The AP is conducted rapidly along the muscle surface and to the interior of the muscle fiber via the membrane of the many transverse tubules (T-tubules) (**Fig. 3.9**). The AP stimulates the release of Ca^{2+} ions from the sarcoplasmic reticulum (SR) of the muscle to initiate contraction of the muscle fiber as a unit (known as excitation–contraction or EC coupling). The relaxation of the muscle fiber is associated with the return of the Ca^{2+} ions to the sarcoplasmic reticulum. The basal lamina of the muscle in the end plate is filled with the enzyme cholinesterase, which inactivates the excess ACh. This enzyme serves two purposes, namely it (1) permits only a small proportion of ACh released to stimulate receptors and their channels on the sarcolemma of the end plate and (2) creates breakdown products, such as choline, which is taken up by the nerve terminals and utilized in the resynthesis of ACh.

Figure 3.8: Structural and molecular features of three types of synapse. **A.** Neuromuscular junction (NMJ, motor end plate). Morphologically the NMJ comprises the motor nerve terminal (M.N.T.) a striated muscle cell (St. M.) and a Schwann cell (S.C.) (Fig. 2.3) that are embryologically derived from three separate sources. The motor nerve arises from the basal plate of the neural tube, the striated muscle from a myotome, and the Schwann cells from a dermatome of a somite (Fig. 6.2). A Schwann cell caps the motor nerve terminal. The basal lamina (B.L.) of the synaptic cleft is a continuum surrounding both the Schwann cell and the motor nerve ending. The thickened postsynaptic membrane contains ionotropic acetylcholine receptors. **B.** Central excitatory asymmetric synapse. The axon terminal is capped by astroglial processes (A.P.). The synaptic cleft lacks a basal lamina. The thickened postsynaptic membrane of the dendritic spine (S) contains ionotropic glutamate receptors. Note the postsynaptic density (PS.D.) and dendritic spine apparatus (S.A.) located in the neck of the spine in Fig. 3.12. **C.** Central inhibitory symmetric synapse. The axon terminal is capped by astroglial processes (A. P.) and the synaptic cleft lacks a basal lamina. The postsynaptic membrane of the dendritic shaft contains ionotropic GABA receptors.


A
Schwann cell
Motor nerve terminal
Basal lamina
Striated muscle
B
Astroglial process
Postsynaptic density
Spine
Spine apparatus
C
Astroglial process
Dendritic shaft

In brief, the neurotransmitter precursor is synthesized within a neuron and stored and packaged in a vesicle within the nerve terminal, and the activated form is released by exocytosis from the vesicle into the synaptic cleft.

Neither Na^+ influx nor K^+ efflux is required for synaptic transmission. Only Ca^{2+} ions, which enter the neuron through voltage-dependent Ca^{2+} channels in the presynaptic ending, are essential. Ca^{2+} ions are the intraneuronal messengers. They serve as the only link to transduce depolarization into all the nonelectrical activities regulated by excitation. Without Ca^{2+} channels, the neurons and, as a consequence, the nervous system would have no outputs. In essence, synaptic delay (i.e., the time interval between the arrival of the action potential at the transmissive segment and the

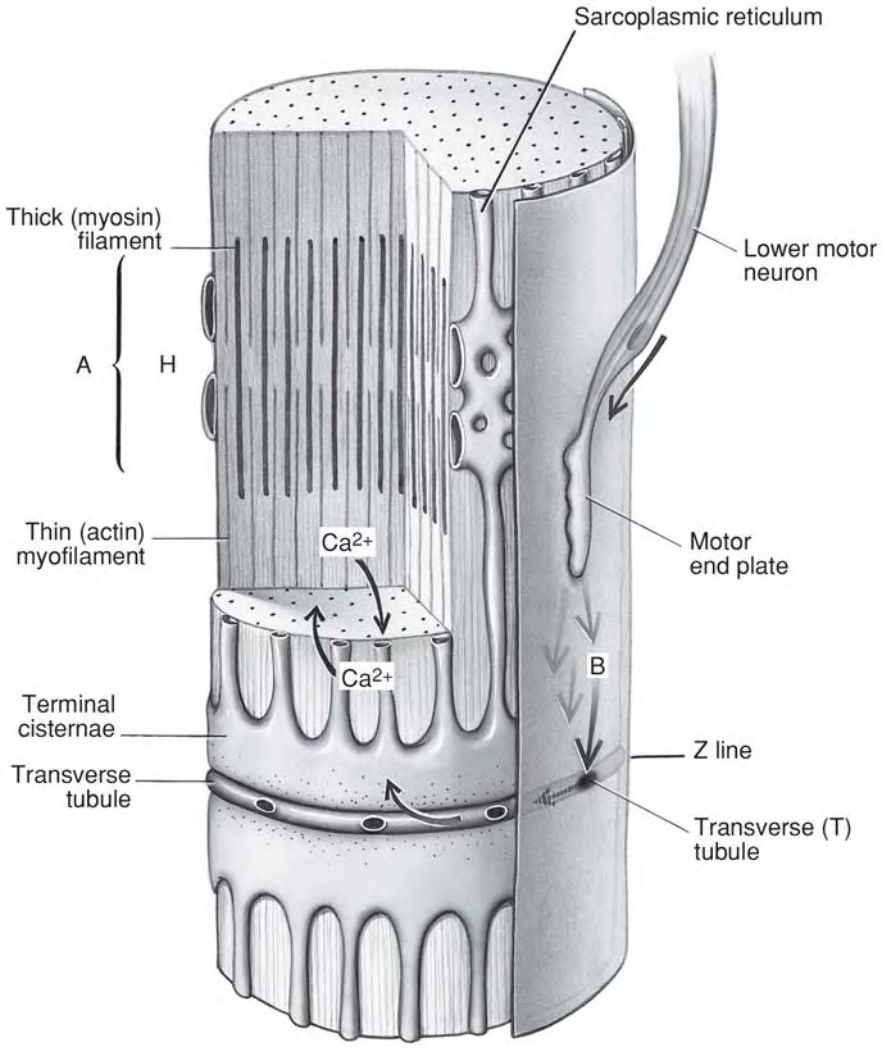


Figure 3.9: Neuromuscular linkage. Sequence of events from the action potential of a motor nerve **(A)**, to motor end plate, to action potential of muscle cell membrane **(B)**, to T-tubule, and to sarcoplasmic cisternae. The release and uptake of calcium ions are involved with excitation-contraction (EC) coupling.

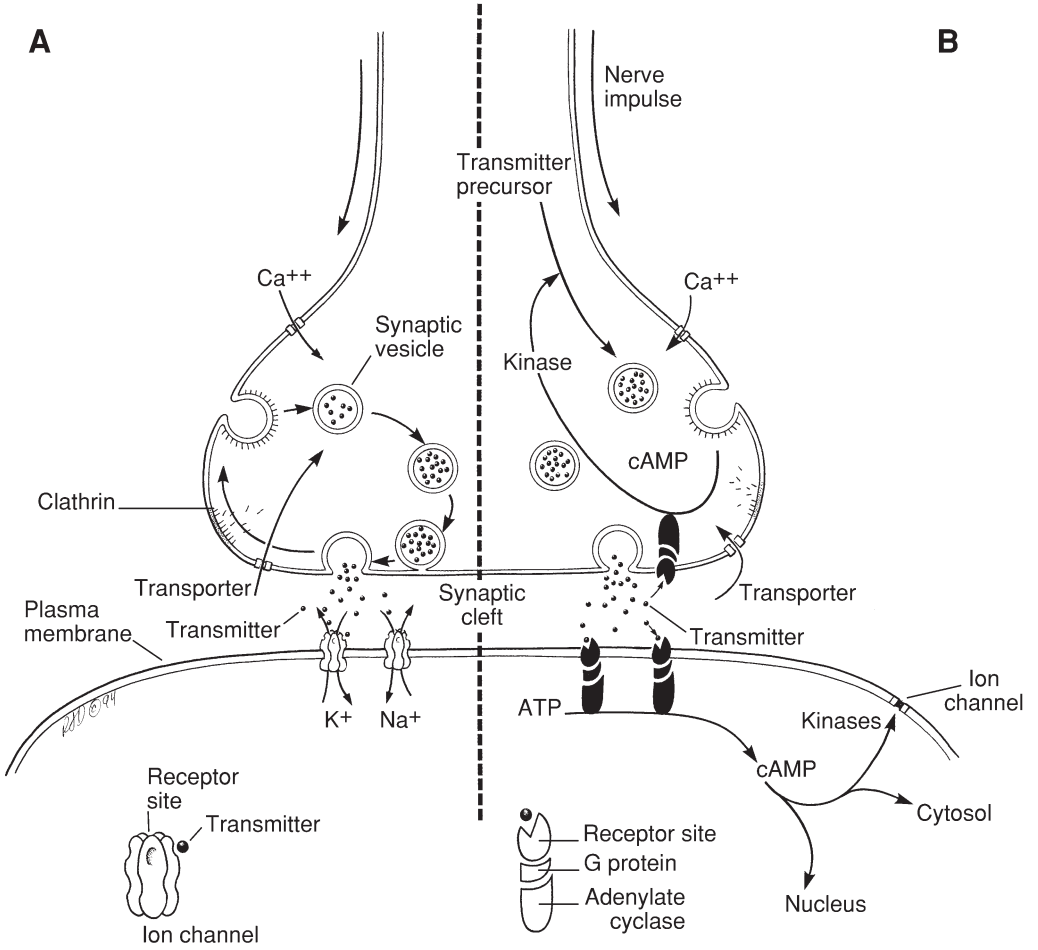


Figure 3.10: A. Chemical synapse—direct gating of an ion channel. In nerve endings, neurotransmitters are packaged in synaptic vesicles and released by exocytosis. Empty synaptic vesicles are rapidly recycled for reuse by endocytosis. The action potential conveyed by the axon depolarizes the nerve terminal to trigger an influx of Ca^{2+} ions through voltage-gated channels. This activates synaptic vesicles to fuse with the presynaptic membrane and to release transmitter molecules into the synaptic cleft by exocytosis. These transmitters diffuse across the cleft and bind to specific receptor sites on the postsynaptic membrane. Each receptor controls an ion channel (selective to specific ions) by direct gating of the ion channels. *The direct gating of an ion channel is mediated by a transmitter receptor that is a part of the ion channel.* The resulting ion flux alters the voltage of the postsynaptic membrane. This can either depolarize the membrane to generate excitatory postsynaptic potentials (EPSPs) or hyperpolarize the membrane to generate inhibitory postsynaptic potentials (IPSPs). Transmitter molecules then uncouple from the receptor sites and, thus, their role in the synaptic response is consummated. The transmitter (or its breakdown product) can be conveyed through a membrane *transporter* into the axon terminal to be recycled. The vesicle membrane is also recycled—the protein *clathrin* becomes transiently associated with the vesicle membrane to assist its being incorporated into a new vesicle by endocytosis. A critical means for sustaining the vesicle population at the endings in the presence of active transmitter release is by the rapid recycling of synaptic vesicles. The entire process, from the activation of the exocytosed synaptic vesicle for recycling until the vesicle with transmitter is competent to be exocytosed again,

release of neurotransmitter) is an expression of the time it takes for the Ca^{2+} ions to diffuse to the site of action within the terminal and the release of transmitter from the synaptic vesicles. At the neuromuscular junction, the normal synaptic potential of –70 mV at the postsynaptic membrane results from the release of about 150 quanta of ACh.

In the innervated muscle fiber, the channels capable of responding to ACh are restricted to the region of the NMJ. Following the denervation of a muscle fiber, the fiber becomes sensitive to ACh over its entire surface. In response to denervation, the fiber synthesizes new ACh-sensitive channels and inserts them into its plasma membrane. In a sense, this is a reversion to its early development when newly differentiated muscle fibers have ACh-sensitive channels scattered over their entire surface. Upon reinnervation, the membrane's ACh sensitivity again becomes restricted to the region of the NMJ.

SYNAPSES AND CHEMICAL TRANSMISSION IN THE CENTRAL NERVOUS SYSTEM

The primary means of communication between neurons is via chemical transmission at synapses. Within the CNS, this process consists of four steps. They are similar in principle to those at the neuromuscular junction, which is actually a synapse between a neuron and a muscle fiber. These steps are (1) synthesis of the transmitter, (2) storage and release of the transmitter, (3) interaction of transmitter with receptors, and (4) removal and recycling of synaptic vesicles and transmitters (**Fig. 3.10**).

For signaling, the nervous system utilizes two classes of neurotransmitter that are contained within vesicles located in the synaptic terminals: (1) small molecule transmitters and (2) neuroactive peptides (Chap. 15). The *small-molecule transmitters* include (a) acetylcholine, (b) the four amino acids glutamate, aspartate, GABA, and glycine, and (c) the four monoamines comprising the catecholamines dopamine, norepinephrine and epinephrine, and the indolamine serotonin. The *neuroactive peptides* include at least 50 different pharmacologically active peptides such as the hypothalamic peptide *somatostatin*, the pituitary peptide *vasopressin*, the digestive system peptide *substance P* and such peptides as *enkephalins*.

Synthesis of the Transmitters

The transmitters are synthesized within the presynaptic neuron. The small-molecule transmitters are generated in all regions of the neuron, including the nerve terminals. Its macromolecular components are synthesized in the cell body

(Figure 3.10 continued)
can presumably occur in less than 3 min. This ensures the maintenance of the population of about 200 vesicles in a single nerve ending. (Refer to the text.) **B.** Chemical synapse—indirect gating of an ion channel via a second messenger. The neuromodulator (transmitter) released from a synaptic vesicle into the synaptic cleft binds with a receptor on the postsynaptic membrane. The receptor activates a G-protein and an intracellular enzyme such as adenylate cyclase. This enzyme converts adenosine triphosphate (ATP) to the second messenger cyclic adenosine monophosphate (cAMP). In turn, cAMP activates other enzymes, called kinases (cAMP-dependent kinases), and phosphorylates ion channels to modulate their function (also to influence activity in the nucleus and the cytosol). Second messengers frequently act through protein phosphorylation to open and close ion channels. *The indirect gating of an ion channel is mediated by a second messenger that couples to the receptor of an ion channel.* Neuromodulators can also bind with autoreceptors located on the presynaptic terminal membrane. These receptors activate the second-messenger system in the axonal terminal to modulate transmitter release. Neurotransmitter transporters are glycoproteins in the cell membrane that are active in reuptake systems conveying neurotransmitters from the synaptic cleft to the axon terminal for recycling. (Refer to the text.)

and rapidly delivered by fast transport to the nerve terminals, where the synaptic vesicles are assembled. Some are derived from released transmitters in the synaptic cleft and recycled back into the terminal. The neuropeptides are generated in the cell body.

Storage and Release of the Transmitters

Once formed, these transmitters are immediately sequestered within the vesicles and tethered to the cytoskeleton in the reserve pool (storage or cytoskeletal anchored compartment) of the nerve terminal. If left free in the cytoplasm, the transmitter is vulnerable to intracellular digestion. Vesicle stores constitute a reserve of transmitters, protected from intracellular enzymes. Thus, only an appropriate level of transmitter is available within the cytoplasm. The small transmitters are stored in *small, clear vesicles* about 50 nm in diameter. Vesicles are then transported to *docking sites* near the sites of release, called *active zones*, where they are docked to *fusion pore complexes* in the presynaptic plasma membrane. The entry of calcium into the nerve terminal through voltage-gated channels triggers the opening of the fusion pore complex and transmitter release into the synaptic cleft. The calcium also mobilizes cytoskeletally anchored vesicles and makes them available for docking with the fusion pore complex.

In contrast to small-molecule vesicle transmitters, the precursors of the neuroactive peptides are synthesized and packaged into secretory granules and synaptic vesicles in the cell body. They are then transported by fast transport via neurotubules to the terminals. In this respect, they are unlike the small-molecule transmitters. The neuropeptides are stored in large (with an electron dense core) vesicles about 120 nm in diameter.

A *transmitter* is a substance that is released at a synapse by a neuron and affects another neuron or effector cell (muscle fiber or glandular cell) in a specific manner. A mature neuron makes use of the same transmitter (or transmitters) at all of its synapses. A small-molecule transmitter and a neuroactive peptide transmitter can coexist in the same mature neuron. The corelease of several transmitters from the presynaptic neuron and the presence of appropriate receptors on the postsynaptic neuron is one expression of the combination of diverse information transfer.

Interaction of Transmitter With Receptors

The released transmitters diffuse quickly across the synaptic cleft, are attracted by and bind to specific receptor proteins on the postsynaptic membrane, and initiate changes in the membrane. There are two general groups of transmitter: *neurotransmitters* and *neuromodulators*.

Neurotransmitters are substances that act directly on the postsynaptic membrane channels and, by altering their permeability, allow ions to pass through the channel mediated by the transmitter receptor that is an integral part of the channel. The neurotransmitters include ACh and the amino acids glutamate, aspartate, GABA, and glycine. They are involved with the generation of fast EPSPs and IPSPs. These local potentials commence within a fraction of a millisecond after the release of the transmitter and seldom persist longer than 100 ms. Glutamate and aspartate are excitatory neurotransmitters and GABA and glycine are inhibitory neurotransmitters. Depending on the nature of the receptor, ACh can act either as an excitatory or inhibitory transmitter.

Some substances released at synapses modify or modulate neural activity rather than initiate it and are called *neuromodulators.* Their effects are of slow onset, but can last for seconds to hours or longer. They operate in the postsynaptic neuron through other molecules called *second messengers* (see later). These long-term changes can be involved with such phenomena as memory and learning. Neuromodulators include the monoamines dopamine, norepinephrine, epinephrine, and serotonin and the neuroactive peptides. Of the many neuropeptides in the brain, most act as neuromodulators.

The receptor protein to which a transmitter binds determines whether it will act as a neuro-

transmitter or a neuromodulator. A substance such as ACh can, depending on the specific receptors, act as both (*see* Second Messenger System).

Removal and Recycling of the Synaptic Vesicles and Transmitters

Vesicle Membrane. In order to release its transmitters into the synaptic cleft, a vesicle containing the transmitters initially fuses with the presynaptic membrane. Following the release by a process known as *exocytosis*, the vesicle membrane becomes incorporated in the presynaptic membrane and coated on its inner surface by a dense layer of the protein *clathrin*. A coated "pothole" is then retrieved as a vesicle by the reverse process of *endocytosis* (**Fig. 3.10**). The budding off of the new vesicle, which is energetically unfavorable, is aided by the clathrin, which remains as a temporary coat around the vesicle. After being pinched off from the plasma membrane, the clathrin-coated vesicles are enzymatically uncoated within a few seconds. Most of the recycled membranes form intermediary structures called *cisternae* before forming vesicles that become filled with newly synthesized or reuptake transmitters. Thus, the vesicle membrane and transmitters are recycled. Some exocytosed vesicle membranes can be returned by retrograde transport to the cell body where they are degraded by lysosomes.

*Removal and Reuptake of Transmitters (**Fig. 3.10**).* Following their release from the nerve terminals, most transmitters are rapidly removed from the synaptic cleft by a sodium-dependent cotransport reuptake system into the axon terminal (or into glial cells). By cotransporting the transmitter with sodium, the energy stored in the transmembrane electrochemical gradients can be used to drive the transmitter back into the axon terminal through the *glycoprotein transporters* in the plasma membrane. Once inside the axon terminal, the transmitter is incorporated into a new synaptic vesicle. Transmembrane transporters, each of which is linked to a specific transmitter, take up neuroactive transmitters such as serotonin, glutamate, aspartate, glycine, GABA, and the catecholamines dopamine and norepinephrine. Transporters are implicated as sites for drug action. Drugs that block neurotransmitter reuptake exert powerful physiologic effects. The action of many antidepressant drugs, such as Prozac, result from the blocking of the serotonin transporter. Thereby, the amount of serotonin in the synaptic cleft is increased (Chap. 15).

The neurotransmitter ACh released from cholinergic endings (e.g., motor end plate) is not taken up into the axon terminal as ACh. Rather it is degraded into choline and acetate by the enzyme cholinesterase located in the basal membrane of the synaptic cleft. The choline is taken up into the axon terminal to be used in the synthesis of new ACh. The choline is combined with *acetyl coenzyme A* (an activated form of acetate) by the enzyme *choline acetyltransferase*, as the catalyst, to become ACh, which is then concentrated in new synaptic vesicles.

Life Cycle of a Synaptic Vesicle: A Summary. The cycle commences with the synthesis of vesicle-associated proteins in the cell body, followed by assemblage of the synaptic vesicle in the axon terminal. Within the terminal, the vesicle undergoes a maturation process involving membrane formation, an endocytosis of transmitter, and the joining to a pool of vesicles tethered to the cytoskeleton. Mobilization from the cytoskeleton is followed by vesicle docking consisting of the approach of the vesicle toward an active zone plasma membrane and the formation of protein complexes linking the vesicle membrane to the plasma membrane. Exocytosis requires an ATP-dependent priming reaction as a prerequisite for Ca^{2+}-triggered membrane fusion. Following the release of the transmitter by exocytosis, the vesicle membrane, protein constituents, and excess transmitter are recycled by endocytosis, mediated, in part, by a clathrin coat, The recycling vesicle sheds this coat and then can directly reuptake transmitter before undergoing the next round of exocytosis.

Activity at the Synapse

Following release, the neurotransmitter molecules diffuse across the synaptic cleft, resulting in a *synaptic delay* of about 1 ms. Depending on the chemical structure of the transmitter and of the receptor sites on the postsynaptic membrane, the resulting permeability changes at the receptor channels lead either to excitation or inhibition. The response of the postsynaptic membrane (excitation or inhibition) cannot be attributed exclusively to the transmitter; the properties of the receptor are also critical. Stimulation of excitatory receptors results in excitatory responses on the postsynaptic membrane, whereas the stimulation of inhibitory receptors results in inhibitory responses. For example, the transmitter ACh stimulates excitatory activity in voluntary muscle and inhibitory activity in cardiac muscle. Neurons generally exert either excitatory or inhibitory influences, but there are other exceptions. As a rule, such transmitters as glutamate, aspartate, and ACh produce excitatory responses, whereas glycine and GABA produce inhibitory responses.

Hormones and drugs can also bind to receptor sites of the plasma membrane. The molecules of neurotransmitters, hormones, or drugs do not just bind to their receptors; each is in a process of binding and unbinding that results in a state of dynamic equilibrium. In this continuous process, each molecule–receptor combination has its own dynamic steady state and rate of binding and unbinding between free and bound molecules and between free and bound receptors. In addition, molecular pumps act quickly to remove the transmitter from the receptor sites.

In summary, two physiologic events occur at a synapse between a transmissive segment and a receptive segment: (1) The nerve impulse by depolarizing the presynaptic membrane brings about Ca^{2+} entry followed by transmitter release into the synaptic cleft and (2) there is a response at the postsynaptic membrane initiated by the transmitter–receptor protein interaction followed by the generation of a graded potential. These two events can be broken down into eight steps: (1) the arrival of the nerve impulse results in presynaptic depolarization, which (2) triggers the opening of calcium channels with an inrush of Ca^{2+} ions through the presynaptic membrane, which (3) triggers transmitter release from presynaptic vesicles, followed by (4) diffusion of the transmitter across the synaptic cleft and (5) the binding of the transmitter to the receptor sites on the postsynaptic membrane, after which there are (6) molecular events in the postsynaptic membrane resulting in (7) the opening of ion channels and (8) the generation of graded postsynaptic potentials. Each of the receptor sites is a complex of proteins with an active binding portion facing the synaptic cleft and channel through the postsynaptic membrane. In effect, the transmitter binds to the receptive site and opens the channel through which the ions flow.

FIRST- AND SECOND-MESSENGER SYSTEMS

Communication between two neurons across a synapse involves first messengers (e.g., neurotransmitters or hormones) released from the presynaptic neuron that interact with two types of receptor on the plasma membrane of the postsynaptic neuron: (1) *ionotropic receptors*, which directly gate (open or close) the ion channels and (2) *metabotropic receptors,* which activate second-messenger systems. Two exceptions to this generalization include (a) gap junctions where ions pass directly between neurons and (b) gaseous messengers (e.g., nitric oxide) that do not act on membrane-bound receptors.

The two main categories of neural *first messengers (* hormones act as first messengers) are based on their mode of action on postsynaptic cells. (1) *Neurotransmitters* interact directly with the *receptors of postsynaptic ligand-gated (transmission-gated) ion channels* (also called *ionotropic receptors).* A ligand is a substance such as a transmitter, hormone, or drug that

binds to a postsynaptic receptor of a channel. (2) *Neuromodulators interact with postsynaptic G-protein-coupled receptor membrane-spanning proteins that are also called metabotropic receptors*. They do not directly open ion channels, but, rather, are linked to *second-messenger systems* by membrane-spanning proteins. These are distinct intracellular biochemical signaling pathways that stimulate or inhibit intracellular responses. Second messenger formation typically is triggered by a first-messenger (transmitter or hormone) acting on a G-protein-coupled cell surface receptor. A second messenger such as cyclic AMP (cAMP) generates a short-lived chemical signal in the cytosol that can trigger a biochemical response that routes its signal via a distinct intracellular signaling pathway (cascade) within the postsynaptic neuron (**Fig. 3.10B**).

An extensive diversity of signaling pathways is present in all neurons. The activation of these pathways is typically initiated by such chemical first-messenger molecular signals as neurotransmitters and hormones. These molecules bind to receptors such as ligand-gated ion channels and G-protein-coupled receptors. The outcome of the activation of these receptors is commonly the production of second messengers, including cAMP, that activate intracellular signaling pathways. In turn, these intracellular signaling pathways convey secondary messengers to the ion channels (with channel pores facing the cytosol), that are directly gated channels at chemical synapses (**Fig. 3.10B**). The result is that signaling pathways generate a vast array of responses over a wide range of times and distances, significantly augmenting and fine-tuning the information-processing ability of neuronal circuits.

Most first messengers can act both as transmitters and modulators, although some act exclusively as one or the other. In common usage, the term "neurotransmitter" (transmitter) often applies to both transmitter and modulator. The transmitters include acetylcholine and small amino acid molecules such as glutamate, GABA, and glycine. The modulators include monoamines (biogenic amines) and neuropeptides such as enkephalin, vasoactive intestinal peptide, and oxytocin (Chap. 15).

The transmitters acting on the synaptic receptor sites of ligand-gated channels are the hallmarks of *fast neurotransmission*. They are fast-acting (millisecond timescale) with *point-to-point* (neuron to neuron) accuracy and provoke either simple excitatory (EPSP) or inhibitory (IPSP) responses (**Fig. 3.5**). These expressions by postsynaptic cells do not depend on the chemical properties of the transmitters but, rather, in the response properties of the receptors. The bulk of specific information processed by the nervous system is associated with synapses that are fast transmission-gated channels opened by first messengers. They are active in most motor actions and perceptual processing within the nervous system.

The *modulators* are first messengers that bind with receptors linked to a membrane-spanning protein unit (e.g., G-protein-coupled receptor; **Fig. 3.10B**) that activates (or inhibits), for example, an intracellular enzyme sequence of adenylyl cyclase and the cyclic adenosine monophosphate (cAMP) kinase phase of a second-messenger cascade. The cAMP cascade is a multistep process that couples the activation of the neurotransmitter receptor by the first messenger, leading to the activation of intracellular enzyme signaling pathways. The G-protein-coupled receptors are members of a large genetic suprafamily. They act through G-proteins (guanine nucleotide-binding proteins) that activate second-messenger intracellular pathways.

Modulation describes the actions of neurotransmitters that do not directly evoke postsynaptic potentials, but, rather, modify or adjust the neuronal responses generated by other synapses (**Fig. 3.10B**). Modulation can alter the properties of the membrane channel proteins through modifying the activity of the ion channels by changing their electrical properties in response to intracellular biochemical changes resulting from synaptic (or hormonal) stimulation. The intrinsic properties of modulation are expressed as slow synaptic transmission (1) neither rapid, nor point-to-point, and not sim-

ply excitatory or inhibitory and (2) achieve effects as typically having a slow onset, usually in seconds, that last for long periods of time (hundreds of milliseconds to minutes, hours, or even longer). Second messengers do not mediate rapid behaviors, but, rather, serve to modulate the strength and efficiency of the ionotropic receptors or the external excitability of the postsynaptic neurons.

Modulation is the term that describes the actions of neurotransmitters that do not directly evoke PSPs but can modify the neuronal response to EPSPs and IPSPs. This is accomplished as follows. In a different channel of the neuron, a second messenger is produced when another first messenger binds to a receptor family. It includes a cascade of certain proteins (e.g., G-proteins) that release a second messenger that, in turn, can trigger a cascade in the cytosol that modifies (e.g., enhances or lowers) quality of the PSPs generated at other channels.

Modulatory Systems

The modulatory form of neurotransmission offers an almost limitless number of ways that neural information encoded by presynaptic impulse activity and conveyed by first-messenger modulators is transformed and used by the postsynaptic neuron. The released modulator interacts with receptors located at the synaptic sites of the postsynaptic membrane to trigger the processing by the modulatory system of the intracellular sequences within the neuronal cytosol The phenomena associated with neuromodulation occur when the neurotransmitter released by a neuron alters the synaptic and cellular properties of another neuron. The effects of neuromodulation are contingent on the activity of the responding neurons. The following are some basic features of how such a system functions (**Fig. 3.10B**). The first-messenger *modulator* binds to a receptor of a plasma membrane spanning complex to activate a transuding intermediate *G-protein* bound to an effector enzyme system that activates *adenylyl cyclase,* an enzyme that catalyzes the conversion of ATP to the quick diffusing small-molecule C-AMP. In turn, C-AMP initiates changes to activate *protein kinases* that phosphorylate (energy-rich phosphate group) such cellular constituents as target proteins. Kinase is an enzyme that uses ATP as a donor of phosphate groups. The concept of phosphorylation mediated by protein kinase is central to the understanding of the second-messenger signaling pathways. The second-messenger system such as cyclic AMP affects cells through the action of protein kinases. Virtually all known cell membrane receptors are linked to intracellular signaling systems that interact first with G-proteins. These include neuromodulatory receptors on neurons, the light-sensitive molecules in photoreceptors, and the odor-sensitive proteins of olfactory neurons. A number of G-proteins that can activate (or inhibit) a variety of intracellular enzymes are known. There are many sequences of first messengers, receptor G-proteins, second messengers, protein kinases, and protein phosphatases that activate or inhibit many cascades of intracellular enzyme systems. These systems act through subtle, complex, and highly integrated biochemical reactions that operate throughout the neuron, including the nucleus (e.g., regulation of gene expression), plasma membrane (e.g., subunits of ion channels), and protein sequences within the networks of the cytoskeleton. Phosphorylation, a reaction in which a phosphate is transferred from ATP into another molecule, of proteins by protein kinases changes their biological activity. Second-messenger-activated kinases catalyze by phosphorylating cellular constituents by activating or inactivating biochemical mechanisms. These sequences can utilize the monorail neurotubules by transporting essential ingredients to their proper locale for functional integration into the sequence. Phosphorylation of ion channels, which alters their conformation slightly, can significantly influence the probability that they will open or close. If the activated kinases are allowed to phosphorylate without some means of reversing the process, the proteins would become fully saturated with phosphate and, thus, regulation would be impossible. Enzymes, called protein phosphatases, can rapidly remove the

phosphate groups. As a consequence the degree of channel phosphorylation at any moment is dependent on the phosphorylation by kinases and dephosphorylation by phosphatases.

Neuromodulators can exert presynaptic as well as postsynaptic effects. Presynaptic terminals have their own receptors, called autoreceptors (**Fig. 3.10B**), which are presynaptic receptors able to recognize and bind with a neuron's own transmitter that has been released. In **Fig. 3.10B**, the autoreceptor is activated to integrate a cAMP cascade to modulate the synthesis of neuroactive agents in the axon terminal. The neuromodulator released by the terminal can regulate, through a feedback sequence, the formation of neuroactive agents in the axon terminal.

General Comments

1. Chemical synapses are the major structure in the brain that allows for the richness of interactions among neurons. Synaptic transmission resulting from the activation of ion-gated channels is simple and fast. Synaptic modulation resulting from activating G-protein receptors is relatively complex and slow. In essence, the G-proteins are signal transducers that communicate signals from many neurotransmitters and hormones. These extracellular signals are received by G-protein-coupled receptors that activate G-proteins. The G-protein pathways route signals from a second messenger (i.e., cAMP) via a number of distinct intracellular signaling G-protein pathways within the neuron. These pathways interact with one another to form a network that regulates ion channels, metabolic enzymes, transporters, and other components of the cellular machinery. They control a broad range of cellular processes including transcription, mobility, contractility, and secretion. These processes, in turn, regulate systems such as embryonic development, homeostasis, learning, and memory.
2. The dynamic networks of second-messenger intracellular enzyme sequences within the dendritic arbors, axon, and cell body of each neuron resemble the complex networks of the brain and spinal cord. Synaptic inputs to the neuron and those to the CNS produce an intricate balancing act of signaling networks, shifting its effects dynamically to the ongoing demands of the (a) neuron or (b) the CNS that vary and are synchronized with alterations of the ever-changing demands of the organism.
3. Learning produces changes in behaviors and motor skills that do not occur by altering the circuitry in the brain, but, rather, by adjusting the strength of synaptic connections between neurons largely via biochemical changes in the neuromodulatory system.
4. Alterations in the modulation of synaptic transmission are involved in
   a. the alterations in mental states caused by drugs such as amphetamines and LSD (lysergic acid diethylamide) and
   b. in afflictions such as schizophrenia.
5. Several second-messenger systems, as well as variations within each of these systems, are known to exist in neurons. Complexities of these systems result from the myriads of linkages involving different types of receptor, G-protein, second messenger, and protein kinase. One estimate suggests that 100 neurons have 1 or more receptor types that communicate with 20 or so G-proteins. The G-proteins are considered to be a key component within the plasma membrane of the complex messenger network within the neuron. The biochemical networks and pathways of enzyme systems within the neuron can expand the neuronal information capacity beyond the currently recognized voltage signals. Thus, these biochemical systems might be potential conduits for information in addition to their current roles of modulating the flow of information.
6. "When one thinks of fast synaptic transmission as being the hardware of the brain and slow synaptic transmission as being the software that controls fast transmission, the molecular basis by which the cells communicate with each other makes sense" (Greengard, 2001).

ELECTRIC (ELECTRONIC) SYNAPSES

Another type of synapse, the electric (electronic) synapse, is relatively rare in the mam-

malian nervous system. In these synapses, there is cytoplasmic continuity between two adjacent neurons through 1.5-nm channels. Because of this continuity, ions can flow between cells at these junctions; these low-resistance "*gap junctions*" result in "*electrically coupled*" neurons. In these synapses, no transmitter is involved. There is essentially no synaptic delay, because the electrical activity readily spreads from neuron to neuron. Because these synapses cannot be modulated, they are not compatible with most neural functions. However, they are occasionally found where activity must be tightly synchronized, as, for example, in the circuits involved with stereotypic saccadic eye movements (Chap. 16), in the junctions (nexus) between smooth muscle cells involved in peristalsis of the gut, and between cardiac muscle fibers (intercalated disks) in synchronizing the heart beat (**Fig. 2.3**).

Because the current can flow across gap junctions in either direction, it might be difficult to decide which is the presynaptic and which is the postsynaptic side of the junction. They can be either, especially when the electric synapse adjoins two dendrites, two cell bodies, or two axons. Evidence suggests that, at some gap junctions, there is only a unidirectional transport of ions.

NEURON AS AN INTEGRATOR

Each neuron is an integrator of stimuli (neurotransmitters) streaming into its dendritic field and onto its cell body (**Fig. 3.11**). Some of the receptive patches (subsynaptic membranes) on the dendrites and cell body are excitatory; others are inhibitory. In addition, as will be described, presynaptic inhibitory activity could indirectly affect some excitatory receptive sites. At any one moment, a neuron might receive hundreds or even thousands of stimuli on its excitatory and inhibitory membrane sites.

Most neurons are under constant *synaptic bombardment*. In this battleground of activity, the neuron reacts and might respond. If the summation of the EPSPs exceeds the summation of the IPSPs, the initial segment of the axon might be excited to initiate the production of an action potential (**Fig. 3.5**). If the algebraic summation of these potentials (EPSPs and IPSPs) is not sufficient to stimulate the initial segment, an action potential is not generated in the axon. The depolarization of the initial segment to the critical voltage is a prerequisite to the generation of an action potential. Thus, each dendrite–cell body complex of a neuron is a *miniature integration center*; it will respond with an action potential according to the net effect of the excitatory and inhibitory synaptic activity on the receptive membrane of the neuron. The axon is the vehicle for signaling coded information, via action potentials, from the dendrite–cell body complex to other neurons or effectors (muscles or gland cells).

Each postsynaptic membrane of the signaled neurons and effectors contains hundreds or even thousands of receptor sites. Each receptor site, which is composed of macromolecular proteins acting as specialized decoders, responds to a given stimulus in its own, probably predetermined way. For example, acetylcholine is an excitatory agent at a motor end plate (contraction of voluntary muscle) and an inhibitory agent at the synapses of the vagus nerve with heart tissue (decrease in heart rate).

A neuron can, in turn, be influenced by its own activity through a *negative feedback loop* involving an interneuron (**Fig. 3.11**). For example, an interneuron called a *Renshaw cell* is intercalated between an axon collateral branch of a lower motoneuron of the spinal cord and the dendrite–cell body region of the same motoneuron, and other motoneurons. The axon collateral terminates at an excitatory synapse on the Renshaw cell; the axons of this cell have, in turn, inhibitory synaptic connections with the parent lower motoneuron (Chap. 10).

Neurons in the CNS may be classified into two major types: (1) projection neurons and (2) local circuit neurons. Projection neurons have long axons coursing from one region of the central nervous system to another. Local circuit neurons have axons passing and interacting with neurons in the immediate vicinity.

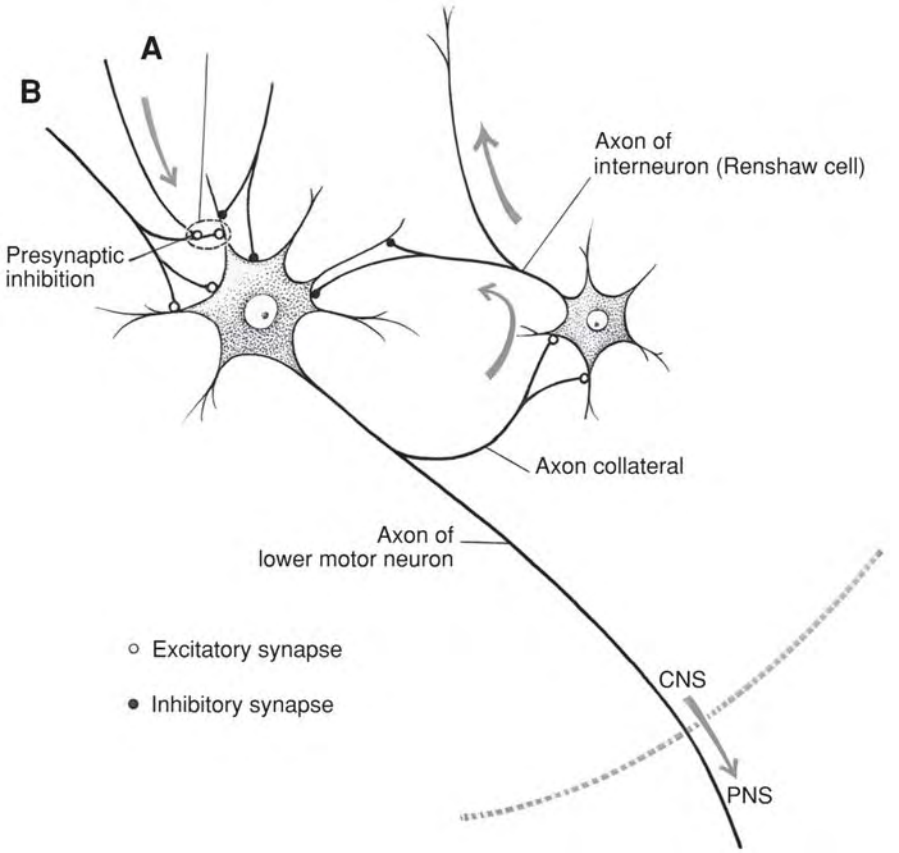


Figure 3.11: The neuron as an integrator. The interrupted line represents the boundary between the central nervous system and the peripheral nervous system. Arrows indicate the direction in which nerve impulses are propagated. Neurons from many sources in the brain, spinal cord, and body convey influences to each lower motor neuron (*see* Chap. 10), which, in turn, innervates some voluntary muscle fibers. The axon collateral of the lower motoneuron excites the interneuron (Renshaw cell), which feeds back inhibitory influences to the lower motoneuron.

There are three types of synapses: **Fig. 3.8(A)** neuromuscular junction (NMJ); **Fig. 3.8(B)** asymmetric central synapse (Gray type 1) and **Fig. 3.8(C)** symmetric central synapse (gray type 2). The *asymmetric* and *symmetric synapses* of the CNS collectively are called *central synapses.* Three features are common to both central synapses and NMJs. All originate developmentally as unspecialized contacts between growth cones and the targets cells (Chap. 6). Both types of synapse are functional at birth, but undergo postnatal alterations. Their ultrastructural and functional roles are essentially similar. They contain pretransmitter-laden vesicles in their presynaptic terminals. Each synapse is capped by glial (astrocyte) or Schwann cell processes. A synaptic cleft separates neurons from each another at a synapse.

Several significant differences do exist between these synaptic types. The quantity and distribution of the synapses on the target cells (neurons or muscle cells) are critical. Each postsynaptic neuron is the target and recipient of *multiple small synaptic inputs* from other

neurons that converge on its dendrites and cell body. In contrast, each postsynaptic striated muscle cell is the target and recipient of a single massive input from *only one NMJ* of a motor neuron. The synapses are markedly different between the two synaptic types. The NMJs are characterized by having a *basal lamina* located within the synaptic cleft that extends as a continuum to envelop both the nerve terminal and the Schwann cell (**Figs. 2.5** and **3.9**). In contrast, the central neuron's synaptic cleft does not have a basal lamina, but might have a slight amount of extracellular matrix. These differences suggest that the functional roles of cell adhesion molecules associated with the matrix of the extracellular clefts differ in these synaptic types. In the NMJs, such molecules as laminins, integrins, and others mediate the cell membrane–matrix interactions. In central synapses, where the extracellular space lacks a basal lamina, cell-to-cell adhesion molecules are mediated by cadherins and others.

The central synapses, functionally designated as excitatory or inhibitory synapses, differ morphologically by the relative thickness between their presynaptic and postsynaptic membranes. The asymmetric synapse has a postsynaptic membrane that is thicker than the presynaptic membrane; functionally, this is usually an excitatory synapse (Gray's type 1; **Fig. 3.8**). The symmetric synapse with its presynaptic and postsynaptic membranes essentially equal in thickness is functionally usually inhibitory Gray's type 2.

The target cells functionally express the nature of the multiple inputs to the central synapses, as contrasted to the solitary input to a muscle cell. The multisynaptic inputs to CNS neurons are essential for the critical role of processing excitatory and inhibitory synaptic inputs. The unitary synaptic input to the NMJ of each voluntary muscle cell acts as a "fail-safe" synapse that ensures a muscle contraction, but lacks the critical qualities of the integrated multisynaptic synaptic inputs that is characteristic of the innervation of each CNS neuron.

PRESYNAPTIC INHIBITION AND PRESYNAPTIC FACILITATION

Presynaptic inhibition is the phenomenon that occurs when a presynaptic neuron (neuron A) exerts inhibitory influences through transmitters at an axoaxonic synapse with the axon terminal of a postsynaptic neuron (neuron B) (**Fig. 3.11**). In turn, this presynaptic inhibition of neuron B depresses the release of excitatory transmitter at the synapse of neuron B with neuron C. In **Fig. 11**, note that the axon terminal of neuron A synapses with the axon terminal of axon B. When terminal B is stimulated alone, EPSPs are evoked in the postsynaptic neuron C. When terminal A is stimulated alone, no response occurs in the terminal B. When A and B are stimulated simultaneously, the generation of EPSPs in the postsynaptic neuron C is decreased.

The explanation for this phenomenon involves the Cl^-, K^+, and Ca^{2+} channels on terminal B. The release of inhibitory transmitter from terminal A opens Cl^- and K^+ channels on terminal B. In turn, this reduces the influx of Ca^{2+} through the voltage-gated channels on terminal A. This reduction of Ca^{2+} influx depresses the release or excitatory transmitter by terminal B at its synapse with the postsynaptic neuron C.

Presynaptic facilitation (presynaptic excitation) is the phenomenon that occurs when a presynaptic neuron (A) exerts excitatory influences through transmitters at an axoaxonic synapse upon the axon terminal of a postsynaptic neuron (B). The presynaptic release of the transmitter is presumed to close the K^+ channels, resulting in a prolongation of the action potential (because of a slower repolarization phase). This acts to increase calcium influx into the postsynaptic axon terminal (neuron B) and thereby enhances excitatory transmitter release by neuron B at its synapse with the postsynaptic neuron C.

The mediation of presynaptic inhibition and presynaptic facilitation through axoaxonic synapses contributes to the elegant neural processing that takes place in the CNS. Of

significance is that axoaxonic synapses can control and alter the Ca^{2+} influx into the axon terminals. As a consequence, presynaptic activity makes it possible to influence selectively the signal transmission from one neuron to another, without affecting the general excitability of the postsynaptic neuron and, thus, its responsiveness to other synaptic inputs.

Importance of Inhibition

Inhibition is a most significant neural activity. It is as important as excitation. The inhibitory neurons and their neural circuits act as governors that prevent, shape, and control the excitatory neurons and their neural circuits from firing to excess. In a simplistic explanation, imagine the consequences of excitatory influences without braking (as the brakes in a car) to keep these influences from getting out of hand. Inhibitory influences function to channel and modulate the effects of excitation and to direct activity to attain a desired end. In learning the intricate movements of writing, a child initially has control difficulties because, in part, too many unnecessary movements are made. During the learning process, these movements are gradually eliminated through inhibition. The desired excitatory channels are sustained to produce the focal movements. In this case, the inhibition of the nonessential movements is significant to the learning process. The inhibitory circuits prevent an excess of neural timing and, in addition, time the specific responsiveness of the excitatory networks. This also applies to neural networks (pathways) that convey and interpret information about the external and internal world. Inhibition, including lateral inhibition, is presumably involved to shape the excitatory activity in the neural pathways that form the basis of the experience of sensation and feeling (sentience) as distinguished from perception and thought.

FUNCTIONAL ROLES OF DENDRITES

"*Dendrites are the brains of the neurons*" *and "the spines are their multifunctional units"* (Shepherd, 1996). They possess the principal receptors and neural processing complexes ("machines") of each neuron (**Fig. 3.12**). Their roles are in part expressed by their characteristic morphological differences in the various regions of the brain and spinal cord. These are features of the diversity and richness of dendritic arborization patterns coupled with the many varieties of spines on their branches (**Fig. 2.2**). Dendritic spines, each usually not more than 1 μm^3 in volume, are diverse in shape and size. However, in vivo imaging observations have demonstrated that spines can form, collapse, reform, and change size and shape rapidly in response to a diverse array of stimuli, and thereby exhibit activity-dependent plasticity (Elhers, 2002).

Of the estimated 10^{14} synapses on the 10^{11} neurons in the human cerebral cortex, over 90% are excitatory axo-dendritic synapses. Excitatory glutamate receptors are present primarily on the dendritic spines and inhibitory GABA receptors are mainly on the dendritic shafts, cell body, and the axon's initial segment. The processing resulting from the stimulation of the ionotropic receptors of the transmission system and the metabotropic receptors of the modulation systems is more complex than that involved in postulated algebraic summation of EPSPs and IPSPs that generates the action potentials of the axon. Some evidence indicates that dendritic synaptic activities are critical in the biochemical mechanisms for regulating the synthesis of synaptic-specific proteins. Some of these proteins are presumably involved in such phenomena as learning and memory (processes by which knowledge of facts, experiences, and skills are acquired and stored).

Dendrites throughout the CNS have roles in processing the neural inputs derived from the sensory receptors. They are integrated and converted into patterns expressed as exquisitely coordinated motor movements. Dendrites contain significant morphologic and functional entities (e.g., spines, postsynaptic densities, and ribosomes) to fulfill their roles within this neurobiologic organization by (1) genetic

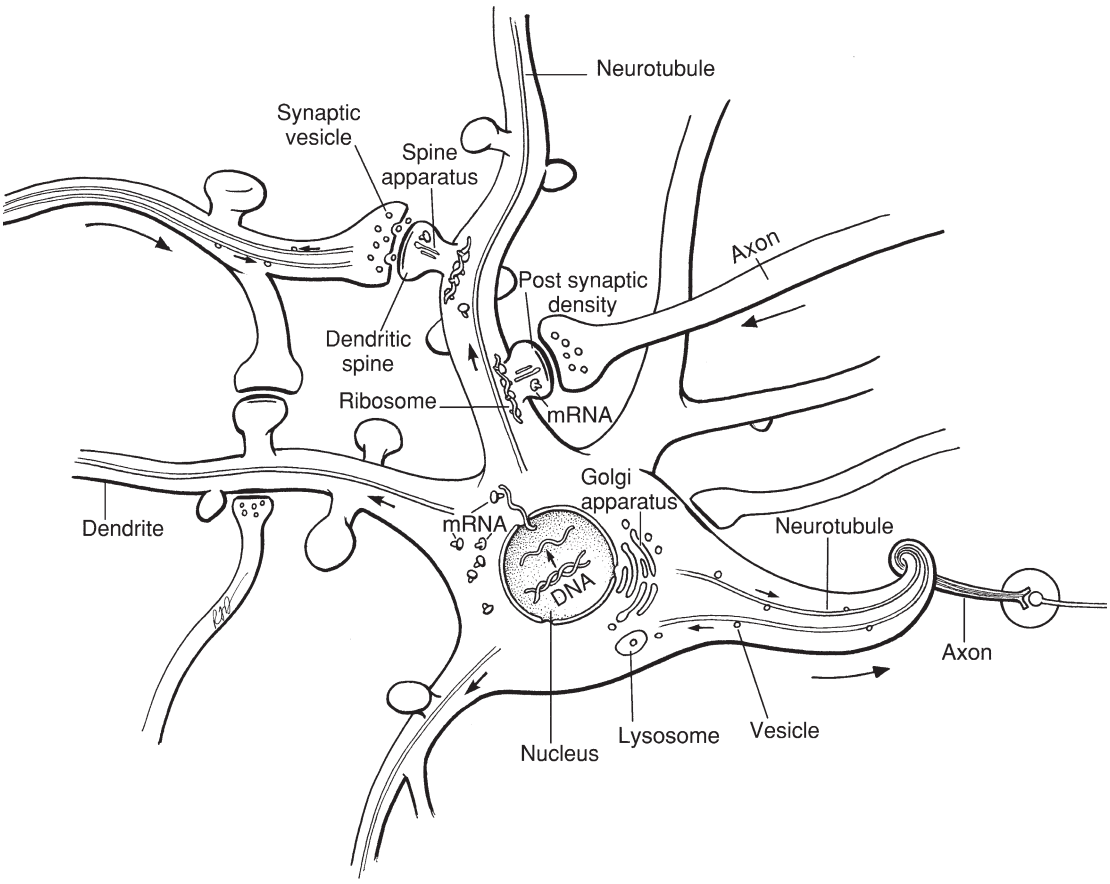


Figure 3.12: The production of synaptic-specific proteins within the multifunctional dendritic spines. Environmental stimuli derived from sources both external to and within the body are monitored by, and the response conveyed by, sensory neurons via an axon to an axon terminal (left side of figure). (1) At the axon terminal, neurotransmitters are released from synaptic vesicles that activate the excitatory asymmetric synapse of a dendritic spine with its postsynaptic density and spine apparatus. *Molecular messengers generated by this synaptic complex are involved in messages from the spine via a retrograde intracellular signaling pathway to transcription regulatory proteins that activate gene expression within the nucleus of the neuron.* The responses are the synthesis by transcription of mRNA, and its passage by nucleocytoplasmic transport through nuclear pore complexes to the cytoplasm. Following binding to ribosomes, the mRNA is transported via neurotubules within the shaft of the dendrite to selected designated "outposts" at the base of dendritic spines. From an "outpost", the mRNA passes into the dendritic spine, where the translation of synaptic-specific protein is thought to occur. (2) At other terminals, the axons of the sensory neurons usually activate inhibitory symmetrical synapses with the dendritic shafts and cell bodies.

Within axons (lower right), the synaptic vesicles migrate by anterograde transport from the Golgi apparatus via neurotubules to the axon terminals. Commencing in the axon terminal, degraded macromolecules are transported as vesicles by retrograde transport via neurotubules of the axon to the lysosomes in the cell body for disposal. Arrows within the neurons designates the direction of transport of ribosomes or vesicles via the neurotubules. Arrows outside of neurons designate the direction of nerve impulses.

(genomic) influences and (2) environmental (epigenetic) influences (Chap. 6). The construction of the basic neuronal networks and their synaptic connections are guided by genetically coded rules, followed by the subsequent fine-honing of these connections from responses to the ongoing environmental influences that translate into a variety of neural adjustments such as plasticity (Chaps. 2 and 6). The effectiveness of synaptic transmission, of the modification of existing proteins, of the synthesis of new proteins, and of plasticity are among the neural phenomena occurring in dendrites continuously being modified with changes in activity and experience (Chap. 25).

The major excitatory transmitter released from the presynaptic terminals of synapses in the CNS is the amino acid L-glutamate. This transmitter excites (1) mainly postsynaptic ionotropic glutamate receptors that directly gate ion channels and (2) metabotropic receptors that indirectly gate channels linked to second messengers. Most glutamate receptors are located on the spines and relatively few on the shafts of dendrites. The fact that each dendritic spine usually accommodates a single synapse suggests that the significance of a spine relates to the creation of a local synapse-specific compartment, rather than as a mere expansion of the postsynaptic surface area (Shepherd, 1996). The consensus is that spines function as microcompartments of chemical signals and regulatory proteins that segregate as well as integrate synaptic signals. An increase in the number of compartments can enhance the informational processing power of dendrites. Some evidence indicates that *retrograde neural signals* from a spine to the presynaptic axon terminal acts to enhance presynaptic function.

The spines have *postsynaptic densities (PSDs)* that are attached to the cytosolic surface of the postsynaptic membrane (**Figs. 3.8** and **3.12**). The PSDs are large protein signaling machines (biochemical signaling pathways) with roles (1) in regulating the strength of synaptic transmission (Kennedy, 2000), (2) in modifying spine morphology, and (3) influencing the synthesis of *synaptic-specific proteins.*

The scaffolding proteins embedded in the PSDs act as linkages for the stimuli from the plasma membrane glutamate receptors (via interaction domains) to the receptors of the smooth endoplasmic reticulum (ER) to receptors of the cytoskeletal actin filaments with their morphogens (types of induction signals) that influence spine shape and size. Each spine has a framework of dense actin filaments, called the *spine apparatus*, that serves as a (1) support and framework for localizing functional molecules, (2) means for propelling ingredients from the shaft of the dendrite to the PSD and in spine motility (**Fig. 3.12**), and (3) source of spine morphogens that influence synaptic function during development and plasticity. Powered by actin filaments, the spines exhibit considerable motility.

The DNA of each neuron's nucleus provides genetically coded information to form messenger RNA (mRNA) that conveys the genetic message through the nuclear pores to the cytoplasm. The mRNAs attached to ribosomes (the genetic message can then be translated into the primary structure of a specific protein by the molecular factories of the ribosomes) migrate via neurotubules (acting like a monorail) to and within the dendritic arbor to locate near the base of and within a spine (**Fig. 3.12**). Molecular triggers activate mRNAs located within the spine for translation to synaptic-specific proteins. Messengers synthesized at the synapse could be involved in an active feedback with the nucleus of the neuron's cell body in modulating DNA transcription. The activity level of the synapses may have a role in regulating the formation of mRNAs, the transport of ribosomes on the neurotubules, and the selection of certain ribosomes to localize adjacent to the appropriate base of spines where the mRNA translation to synaptic-specific proteins is sustained and regulated (alternate terms include ribopolysomes or synapse-associated polyribosomes that are mRNAs with added ribosomes engaged in protein production). Biologists traditionally view the nucleus as the command center supplying mRNAs translation into protein. Neurons might have slightly modified this

strategy by the synthesis of proteins in spines, and thereby exert influences on synapse-specific protein production in consort with other related synapses. This effect by a synapse might be another factor that enables the nervous system to utilize the neural information received for strengthening specific synapses with fresh proteins for a variety of neuronal activities. It is even possible that certain proteins are uniquely involved in learning and memory. In essence, the functional activities of the synapses, PSD signaling machines, mRNA production, and synapse-specific proteins are integrated by homeostatic integration with the neuron's nucleus, by which intraneuronal signaling cytoskeletal pathways from the spine communicate with the nucleus (**Fig. 3.12**). Indications are that active synapses of the spine have a significant role in the regulation of translation and in the direction of transport of a ribosome to a spine. Although the synapse-specific proteins produced might contribute to learning and memory; the linkage between dendritic protein synthesis and learning and memory, as yet, has not been established. Synapses that undergo long-lasting changes in strength are likely to contribute to learning and memory. Thus, the dendritic spines function as the recipients of (1) neural information via their synapses from both the external environment and from the internal environment of the body and (2) genomic information from the neuron's nucleus, This is consistent with the role of the spines as multifunctional units of the dendrites as the brains of the neurons. In neurons, gene expression involves a distributed network of translating machines in a functional group of neurons. The polyribosomes are positioned near synapses and translate populations of mRNAs within selected spines. The localization of translation machinery and mRNA at synapses endows individual synapses with the capability of independently controlling synaptic strength through the local synthesis of proteins. The newly synthesized protein presumably has roles in replacing degraded proteins, increasing the levels of existing proteins or even in creating novel proteins.

Relation of the Morphological and Functional Parameters of Dendritic Spines

Spines are dynamic morphological specializations that receive experience-derived synaptic input, and following molecular microprocessing with DNA derived ribosomes, they (mRNA polyribosomal complexes) generate synaptic-specific proteins. The vast variety of forms and shapes of spines (Fiala and Harris, 1999; **Fig. 2.2**) are presumably expressions of the many multifunctional units within the spines (Shepherd, 1996). For example, the volume of the spine head is directly proportional (1) to the number of postsynaptic receptors and (2) to the number of docked synaptic vesicles in the presynaptic terminals (Yeste and Bonhoeffer, 2001). This association of *structure* (*form*) *and function* can be correlated with changes in the lengthening, shortening or widening of the neck adjacent to the dendritic shaft, with changes in the size and shape of the head of the spine, and with changes in the formation of new spines. Many changes have been associated with synaptic plasticity.

SOME GENERAL CONCEPTS ASSOCIATED WITH CODING AND NEURONAL PROCESSING IN THE NERVOUS SYSTEM

Neural Signals: Label Line Codes and Pattern Codes (Fig. 3.13)

The body responds to external and internal environmental stimuli through receptors that are associated with modalities of the sensory systems. The recognized receptors are mechanoreceptors, nociceptors, thermoreceptors, photoreceptors, and chemoreceptors. The modalities comprise general somatic senses, balance, audition, vision, taste, and smell. Most sensory receptors are sensitive to specific stimulus energies, called receptor specificity that results in generating a neural signal as a *signal-line code* in a first-order neuron. The code of specific modalities associated with, for example, touch (Chap. 10) is conveyed via specific

lines though a series of neurons and neural centers of the CNS where they are processed to evoke the perception of the sensation. Each sensory receptor responds when it is adequately stimulated, in a specific manner regardless of the stimulus. Whether activated by a natural or an artificial (e.g., electrical) stimulus, the same sensation is elicited. Chemoreceptors lack the specificity of responding to a single stimulus signal and, thus, do not project their information along signal lines. Rather, the modalities associated with taste and smell use a *pattern code* signal in which several receptors are activated. The resulting discharge pattern of signals formed by a group of neurons is the basis for the perception of a given flavor or odor.

Transformation of the Neural Signals at Processing Centers of Pathways

Neural processing occurs within the neural centers (laminae, nuclei, and cortices) of each pathway system. Neurons within these centers process the patterns of incoming signals and transform them so that the relay neurons project a different pattern of signals to other centers. *Each center performs a transformation function.* Each center consists of (1) relay neurons whose axons project to other centers, (2) interneurons with processes located wholly within the center, and (3) terminations of axons from other sources.

Processing Within the Nervous System

The ascending (and descending) pathways function both as processors and as transmitters of coded information. The processing within a center of a pathway is information linked, not energy linked. For example, stimulation of the optic system evokes sensations related to vision, regardless of whether the stimulus is light, an electrical shock, or a blow to the eye.

The sensory inputs to the relay neurons within a center are examples of convergence (input of axons from many neurons to one relay neuron) and divergence (input of an axon to more than one relay neuron). These inputs form a basis for some of the complexities of interactions among neurons. The numerous signals arriving at each processing center and interaction with the local interneurons act to bias, enhance or dampen signals and their transmission. In effect, each center acts as an editor. A major role in the processing is performed by the local inhibitory interneurons in (1) feedback inhibition, (2) feed-forward inhibition, and (3) reflected inhibition.

Feedback (or Recurrent) Inhibition (Fig. 3.13)

In feedback inhibition, the most actively firing relay neurons, utilizing inhibitory interneurons, depress the activity of the adjacent, less actively firing relay neurons. Thus, the more active neurons enhance and amplify the contrast between the actively firing relay neurons and their less active neighbors. This leads to a selective emphasis of one stimulus over another. Stated differently, the signal is enhanced and the adjacent noise of the less active neurons suppressed. It is called feedback or recurrent inhibition because the recurrent collateral branches of the axon of the relay neuron feed back to excite inhibitory interneurons causing inhibition of the adjacent relay neurons.

Feed-Forward (or Reciprocal) Inhibition (Fig. 3.13)

In feed-forward inhibition, the activity of one or more neurons inhibits another neuron or group of neurons. This acts in what is called the *singleness of action* in which only a limited number of competing responses are expressed and others are suppressed. The feed-forward neuronal circuits consist of the branches of the axons of relay neurons entering a nucleus and terminating by synapsing with local circuit interneurons. In turn, these neurons exert inhibitory influences upon relay neurons via either presynaptic or postsynaptic inhibition. *Presynaptic inhibition* occurs when the axons entering a relay nucleus synapse with excitatory local circuit interneurons that, in turn, synapse with the terminals of neighboring entering axons. *Postsynaptic inhibition* occurs when the axons entering the nucleus synapse with local interneurons that, in turn, synapse

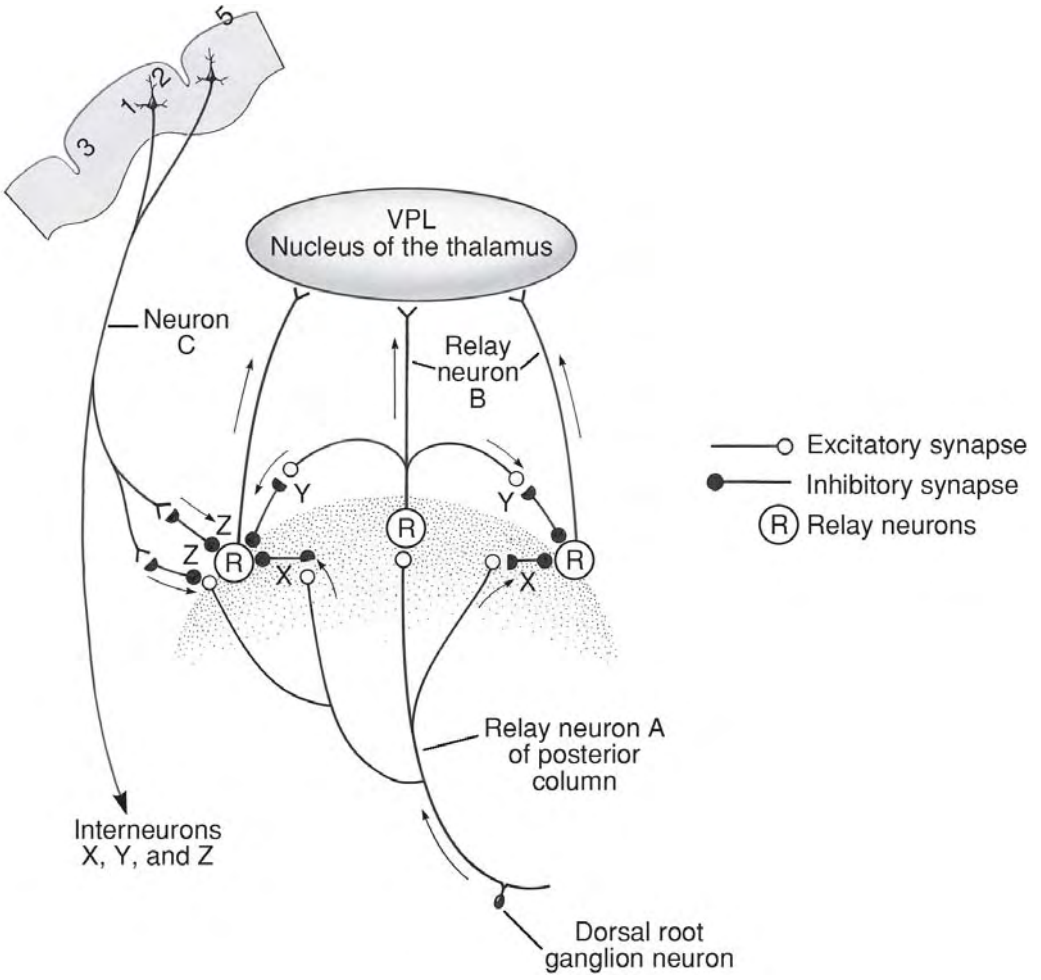


Figure 3.13: Diagram illustrating three types of neural processing involving inhibition. The neurons represent relay (R) neurons and local inhibitory neurons (X, Y, and Z) associated with the nuclei gracilis and cuneatus of the posterior column–medial lemniscus pathway (Chap. 10). The relay neurons (R) project to the ventral posterior lateral nucleus (VPL) of the thalamus.

1. Feed-forward inhibition. Relay neuron A of a dorsal root ganglion has an axon that ascends to and diverges within the nuclei gracilis and cuneatus into branches that have excitatory synapses with several neurons (shaded area). These feed-forward to excite the relay neurons (R) and, in addition, local inhibitory interneurons (X). The latter inhibit adjacent relay neurons.
2. Feedback inhibition. Relay neuron (B) has recurrent branches that feedback to excite local inhibitory interneurons (Y). The latter inhibit the adjacent relay neurons.
3. Reflected inhibition. Neurons (C) of the somatic sensory areas 3, 1, 2, and 5 of the cerebral cortex (C) have long axons that excite local inhibitory interneurons (Z). The latter modulate the relay neurons by both presynaptic and postsynaptic inhibition. (Adapted from Kandel, Schwartz, and Jessell).

with the cell bodies of adjacent relay neurons. A *feed-forward inhibitory circuit* is characterized by having one or more inhibitory interneurons within the circuit. These interneurons convey influences in a *forward direction* toward the more distal levels of the pathway. Because these inhibitory circuits utilize ascending or afferent relay neurons, their activity is referred to as *afferent inhibition.*

Feed-forward inhibition is utilized by the influences of muscle spindles in the stretch reflex (Chap. 8). The afferent fibers from neuromuscular spindles excite inhibitory interneurons that exert inhibitory influences upon the alpha motoneurons innervating voluntary muscles.

An expression of feed-forward inhibition is known as *lateral* or *surround* inhibition. This physiologic activity is utilized by all sensory systems in processing neural information. For example, to discriminate between two points close together (*see* Two-Point Discrimination, Chap. 10) the two signal lines for the two points are each maintained in order for the perception to occur. Each signal line enhances its signal and suppresses the surrounding relay neurons in order to maintain its identity. *Inhibitory interneurons* interact with adjacent relay neurons with the result that the *signal-to-noise* is enhanced. In effect, the excitatory neurons of the circuit or pathway convey the signal and also stimulate the inhibitory interneurons in adjacent (lateral) locales to suppress the circuits conveying the noise within the sensory pathway. This emphasis on the signal and suppression of the noise is also known as the *focusing effect* or *sharpening effect*. For example, background noise such as potential sound generated by blood flow through the inner ear is not normally heard because it is filtered out by lateral inhibition within the auditory pathways, and the neural activity associated with the sound to be perceived is increased. In the visual system, inhibitory interneurons have a role in enhancing information to heighten the contrast, to make borders and contours more pronounced to the viewer and in the generation of the center-surround receptor fields (Chap. 19).

Reflected (or Distal) Inhibition (or Excitation) (Fig. 3.13)

This type of feedback involves descending centrifugal fibers (reflected descending fibers) from the rostrally located cerebral cortex and brainstem nuclei to the more caudally located nuclei of the ascending pathways. Some influences might be projected from the brainstem and spinal cord via fibers known as efferents to some sensory receptors. These descending fibers generally form excitatory synapses with inhibitory interneurons. Cortical and brainstem neurons can regulate, through inhibition, the information flow into the relay nuclei. This so-called distal inhibition can express itself by exciting interneurons that modulate the relay neurons through both inhibitory presynaptic and postsynaptic synapses. By this means, the higher centers of the brain can control the sensory input from the peripheral receptors to the relay nuclei (Chap. 10). Efferent neurons, with their cell bodies in the brainstem and spinal cord, which send axons to sensory receptors, can facilitate or inhibit and thus alter the receptivity of the receptors. The gamma efferent fibers to the neuromuscular spindles (Chap. 8) and the cochlear efferent fibers to the organ of Corti (Chap. 16) are examples of such feedback neurons.

SUGGESTED READINGS

Araque A, Carmignoto G, Haydon PG. Dynamic signaling between astrocytes and neurons. *Annu. Rev. Physiol.* 2001;63:795–813.

Chen YA, Scales SJ, Scheller RH. Sequential SNARE assembly underlies priming and triggering of exocytosis. *Neuron* 2001;30:161–170.

Cline HT. Dendritic arbor development and synaptogenesis. *Curr. Opin. Neurobiol.* 2001;11:118–126.

De Camilli P, Takei K. Molecular mechanisms in synaptic vesicle endocytosis and recycling. *Neuron* 1996;16:481–486.

Dowling J. *Neurons and Networks: An Introduction to Neuroscience.* Cambridge, MA: Harvard University Press, 1993.

Eccles JC. The synapse: from electrical to chemical transmission. *Annu. Rev. Neurosci.* 1982; 5:325–339.

Eccles JC. Developing concepts of the synapses. *J. Neurosci.* 1990;10:3769–3781.

Ehlers MD. Molecular morphogens for dendritic spines. *Trends Neurosci.* 2002;25:64–67.

Ehlers MD. Eppendorf 2003 prize-winning essay. Ubiquitin and the deconstruction of synapses. *Science.* 2003;302:800–801.

Farsad K, De Camilli P. Neurotransmission and the synaptic vesicle cycle. *Yale J. Biol. Med.* 2002; 75:261–284.

Fenstermaker V, Chen Y, Ghosh A, Yuste R. Regulation of dendritic length and branching by semaphorin 3A. *J. Neurobiol.* 2004;58:403–412.

Fiala JC, Harris KM. Dendritic structures. In: Stuart G, Sprutson N, Hausser M, eds. *Dendrites.* New York: Oxford University Press; 1999.

Fields RD, Stevens-Graham B. New insights into neuron–glia communication. *Science* 2002;298: 556–562.

Gorlich D, Kutay U. Transport between the cell nucleus and the cytoplasm. *Annu. Rev. Cell Dev. Biol.* 1999;15:607–660.

Greengard P. The neurobiology of slow synaptic transmission. *Science.* 2001;294:1024–1030.

Hannah MJ, Schmidt AA, Huttner WB. Synaptic vesicle biogenesis. *Annu. Rev. Cell Dev. Biol.* 1999;15:733–798.

Hering H, Sheng M. Activity-dependent redistribution and essential role of cortactin in dendritic spine morphogenesis. *J. Neurosci.* 2003;23: 11,759–11,769.

Ingolia NT, Murray AW. Signal transduction. History matters. *Science* 2002;297:948–949.

Jan LY, Stevens CF. Signalling mechanisms: a decade of signalling. *Curr. Opin. Neurobiol.* 2000;10:625–630.

Kandel ER. The molecular biology of memory storage: a dialogue between genes and synapses. *Science* 2001;294:1030–1038.

Kandel E, Schwartz J, Jessell T, editors. *Principles of Neural Science.* 4th ed. New York, NY: McGraw Hill; 2000.

Katz PS, Clemens S. Biochemical networks in nervous systems: expanding neuronal information capacity beyond voltage signals. *Trends Neurosci.* 2001;24:18–25.

Kennedy MB. Signal-processing machines at the postsynaptic density. *Science* 2000;290: 750–754.

Li Z, Sheng M. Some assembly required: the development of neuronal synapses. *Natl. Rev. Mol. Cell Biol.* 2003;4:833–841.

Lin RC, Scheller RH. Mechanisms of synaptic vesicle exocytosis. *Annu. Rev. Cell Dev. Biol.* 2000;16:19–49.

Littleton JT, Sheng M. Neurobiology: synapses unplugged. *Nature* 2003;424:931–932.

Maletic-Savatic M, Malinow R, Svoboda K. Rapid dendritic morphogenesis in CA1 hippocampal dendrites induced by synaptic activity. *Science* 1999;283:1923–1927.

Mattson M. Neuroprotective signal transduction. Totowa, N.J: Humana Press.

Murthy VN, De Camilli P. 2003. Cell biology of the presynaptic terminal. *Annu. Rev. Neurosci.* 1998;26:701–728.

Nimchinsky EA, Sabatini BL, Svoboda K. Structure and function of dendritic spines. *Annu. Rev. Physiol.* 2002;64:313–353.

Reith MEA ed. *Cerebral Aignal Transduction: From First to Fourth Messengers.* Totowa, NJ: Humana; 2000.

Reith MEA, ed. *Neurotransmitter Transporters: Structure, Function, and Regulation.* Totowa, NJ: Humana; 2002.

Sheng M, Kim MJ. Postsynaptic signaling and plasticity mechanisms. *Science* 2002;298: 776–780.

Shepherd GM. The dendritic spine: a multifunctional integrative unit. *J. Neurophysiol.* 1996; 75:2197–2210.

Song H, Stevens CF, Gage FH. Astroglia induce neurogenesis from adult neural stem cells. *Nature* 2002;417:39–44.

Yasuda R, Sabatini BL, Svoboda K. Plasticity of calcium channels in dendritic spines. *Nature Neurosci.* 2003;6:948–955.

Yuste R, Bonhoeffer T. Genesis of dendritic spines: insights from ultrastructural and imaging studies. *Natl. Rev. Neurosci.* 2004;5:24–34.

Zucker RS, Regehr WG. Short-term synaptic plasticity. *Annu. Rev. Physiol.* 2002;64:355–405.

4
Blood Circulation

Arterial Supply
Venous Drainage
Functional Considerations
Blood–Brain Barrier

Although the brain accounts for only 2% of the body weight of a 175-lb human, its survival and functioning depend on continuously receiving 20% of the arterial blood flow from the heart, metabolizing 20% of the available oxygen, and generating 20% of the bodily energy. This level of energy consumption is sustained by the high and privileged rate of the flow of blood with its glucose and oxygen to the brain as compared to other organs. The high metabolic activity and high oxygen consumption are characteristic of cerebral metabolism that derives its energy largely from glucose, the basic energy substrate of the brain. Glucose is metabolized through glycolysis, Krebs' citric acid cycle, and the respiratory (electron transport) chain. In aerobic respiration, the combination of glucose and oxygen produces energy, CO_2, and H_2O. Mitochondria carry out aerobic respiration that generates ATP (adenosine triphosphate), which serves as the cell's powerhouse. The chemical energy stored as high-energy phosphate bonds in ATP is the constant source of energy obtained from the conversion of ATP to ADP (adenosine diphosphate).

The energy utilized that is derived from glucose in the blood and changes in its consumption can be measured using the method of *positron-emission tomography* (PET, Chap. 26). This technique depends on the detection of radiation, mainly positrons, released from short-lived radioactive atoms by an array of radiation detectors positioned around the subject's head. The procedure involves the rapid synthesis of marker molecules of glucose containing the radioactive molecules, *labeled glucose*, following the injection of the radioactive glucose injected into an arm vein and monitored by the scanning of the head to map the distribution of the glucose in the brain. Rapid repetition allows differences between brain structures to be detected and related to the type of "work" each portion of the brain is doing at that time. Labeled glucose accumulates in neurons doing the "brain" work. Roughly 800 mL of blood flows through the brain each minute, with 75 mL present within the brain at any moment. Each day, the brain utilizes about 400 kcal, or about one-fifth of a 2000-kcal diet. It takes about 7 seconds for a drop of blood to flow through the brain from the internal carotid artery to the internal jugular vein. The necessity for this continuous flow is because the brain stores only minute amounts of glucose and oxygen and derives its energy almost exclusively from the aerobic metabolism of glucose delivered by the blood. Paradoxically, this blood circulation is the minimum required; consciousness is lost if the blood supply is cut off for less than 10 seconds. The demand for blood is the same whether one is resting, sleeping, thinking, or exercising.

Neurons differ from cells of other organs in their requirements for oxygen. Deprived of oxygen, neurons almost always die within a few minutes. Neurons cannot build an oxygen debt, as can muscle and other body cells, that is, they cannot survive anaerobically. This constraint has enormous medical implications. When the oxygen supply is cut off following a

heart attack or suffocation, the brain dies first. Only if oxygen is restored to the brain in a few minutes will the brain retain its functional viability.

Blood is supplied to the brain by the internal carotid arteries and the vertebral arteries. It is drained from the brain largely by the internal jugular vein. The cerebral arteries, venules, and veins do not differ structurally from vessels of similar size and function in other organs. However, the capillaries of the central nervous system (CNS) do differ significantly in ultrastructure and physiology from capillaries of the general circulation (*see* Blood–Brain Barrier).

ARTERIAL SUPPLY

The arterial blood supply to the brain is derived from two pair of trunk arteries: (1) the vertebral arteries and (2) the internal carotid arteries (**Figs. 4.1** and **4.2**).

Vertebral Circulation

The paired *vertebral arteries* enter the cranial cavity through the foramen magnum and become located on the anterolateral aspect of the medulla (**Fig. 4.1**). They unite at the midline at the pontomedullary junction to form the *basilar artery*, which continues to the midbrain level, where it bifurcates to form the paired *posterior cerebral arteries*. The branches of the vertebral and basilar arteries supply the medulla, pons, cerebellum, midbrain, and caudal diencephalon. Each posterior cerebral artery supplies part of the caudal diencephalon and the medial aspect (and adjacent lateral aspect) of the occipital lobe including the primary visual cortex (area 17) and the inferior posterior temporal lobe. The

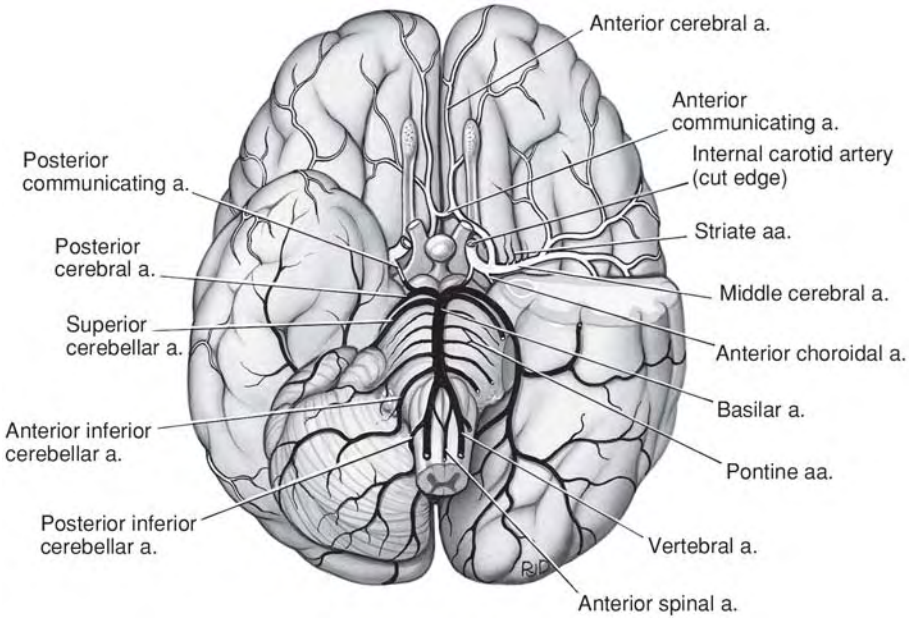


Figure 4.1: Major arterial supply to the brain. The vertebral–basilar–posterior cerebral arterial tree is indicated as solid black vessels and the paired middle and anterior cerebral tree is indicated as white vessels. Note the circle of Willis, which comprises the single anterior communicating artery and the paired anterior cerebral, internal carotid, posterior communicating, and posterior cerebral arteries. The last paired arteries are formed by the bifurcation of the basilar artery. The circle of Willis is located beneath the hypothalamus and surrounds the stalk of the hypophysis and optic chiasm.

branches of the vertebral and basilar arteries that supply the medial aspect of the brainstem adjacent to the midsagittal plane are called *paramedian arteries (anterior spinal artery, paramedian branches of the basilar artery)*; those that supply the anterolateral aspect of the brainstem are called *short circumferential arteries (branches of the vertebral artery, short pontine circumferential branches of the basilar artery)*; and those that supply the posterolateral and posterior aspect of the brainstem and cerebellum (**Figs. 17.1** and **17.2**) are the *long circumferential branches (posterior spinal artery, posterior inferior cerebellar artery, anterior inferior cerebellar artery, superior cerebellar artery)*.

Internal Carotid Circulation

Each *internal carotid artery* passes through the cavernous sinus as the S-shaped carotid siphon and then divides, level with and lateral to the optic chiasm, into two terminal branches: (1) the *anterior cerebral artery*, which supplies the orbital and medial aspect of the frontal lobe and medial aspect of the parietal lobe, and (2) the *middle cerebral artery*, which passes laterally through the lateral fissure between the temporal lobe and insula and divides into a number of branches supplying the lateral portions of the orbital gyri and the frontal, parietal, and temporal lobes (**Figs. 4.1** and **4.3**). Peripheral branches of the middle cerebral arteries anastomose on the lateral surface of the cerebrum with peripheral branches of the anterior and posterior cerebral arteries. Branches of the middle cerebral artery and the choroidal arteries penetrate the cerebrum to supply the basal ganglia, most of the diencephalon, internal capsule, and adjacent structures; these central or ganglionic branches (e.g., striate arteries) and the choroidal arteries are variable in their extent and in their anastomotic connections. Other branches of the internal carotid arteries include the *ophthalmic artery* (to the orbit), the *anterior choroidal artery* (to the arc structures adjacent to the choroidal fissure; Chap. 5), and the *posterior communicating artery* (joins posterior cerebral artery).

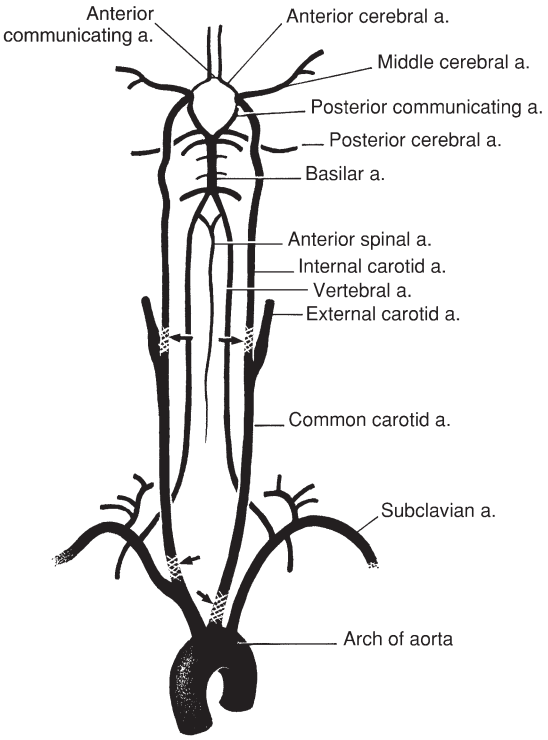


Figure 4.2: Cerebral arterial circle (circle of Willis). The *cerebral arterial circle* consists of the following: (1) the proximal part of three major paired arteries: anterior, middle and posterior cerebral; (2) the short, single anterior communicating artery that connects the anterior cerebral arteries; and (3) the longer, paired posterior communicating arteries that go between the middle and posterior cerebral arteries. The circle of Willis is supplied by two pairs of arteries (a) the vertebrals—branches of the subclavian arteries and (b) the internal carotids—branches of the common carotid arteries. Each internal carotid artery divides into an anterior cerebral artery and a larger middle cerebral artery. The arrows point to common sites of atherosclerosis and occlusion.

Circle of Willis

Although the *vertebral–basilar arterial tree* and the *internal carotid arterial tree* are essentially independent, there are some anastomotic connections between the two systems (e.g., between the terminal branches of posterior

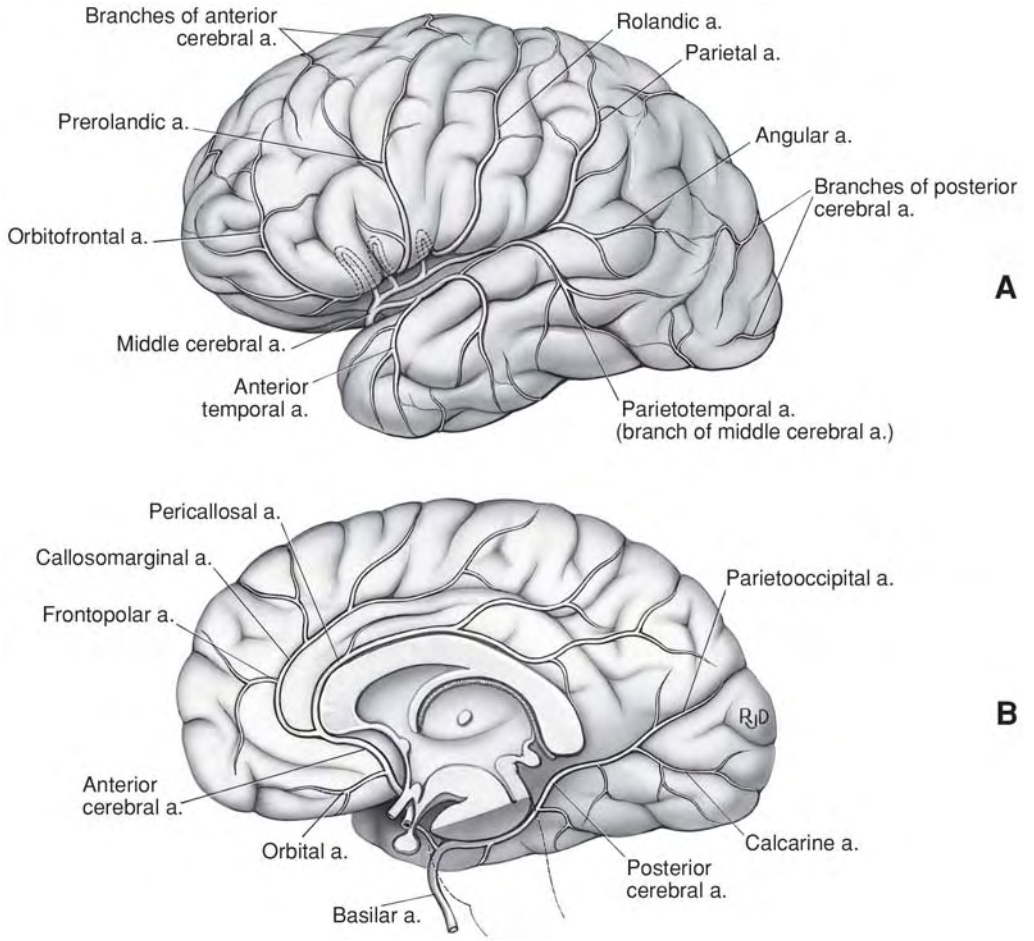


Figure 4.3: Distribution of the arteries on the surface of the brain. **(A)** lateral surface; **(B)** medial surface. Superior cerebellar artery.

cerebral arteries and those of the anterior and middle cerebral arteries). The *cerebral arterial circle of Willis* (**Figs. 4.1 and 4.2**) is an arterial ring in which the two systems are connected by the small posterior communicating arteries. The anterior communicating artery that connects the two anterior cerebral arteries completes the circle. There is actually little exchange of blood through these communicating arteries; the circle of Willis can act as a safety valve when differential pressures are present among these arteries.

The arteries meeting at the cerebral arterial circle of Willis form branches comparable to those of the basilar artery. Thus, (1) the anterior, middle, and posterior cerebral arteries are actually long circumferential arteries, (2) the subbranches (e.g., striate arteries; **Fig. 4.1**) of these three major cerebral arteries close to the circle of Willis are short circumferential branches, and (3) the small medial arteries arising from the circle of Willis are paramedian branches.

Anastomotic connections within the vertebral and internal carotid systems are extensive in the brain. Those that occur among the large branches of the superficial arteries on the surface are usually physiologically effective, so

that occlusion need not result in impairment of blood supply to the neural tissues. Rich anastomoses do exist among the capillary beds of adjacent arteries within the substance of the brain, but occlusions of these arteries most often are followed by neural damage. The anastomotic connections might not be sufficient to allow adequate blood to reach the deprived region rapidly enough to meet its high metabolic requirements.

VENOUS DRAINAGE

The veins draining the brainstem and cerebellum roughly follow the arteries to these structures. On the other hand, the veins draining the cerebrum do not usually form patterns that parallel its arterial trees. In general, the venous trees in this region have short stocky branches that come off at right angles, resembling the silhouette of an oak tree.

Dural Sinuses

Venous anastomoses are extensive and effective between deep veins within the brain and superficial surface veins (**Fig. 4.4**). The veins of the brain drain into superficial venous plexuses and dural sinuses. The *dural (venous) sinuses* are valveless channels located between two layers of the dura mater. Most venous blood ultimately drains into the *internal jugular veins* at the base of the skull.

The blood from the cortex on the upper, lateral, and medial aspects of the cerebrum drains into the *superior sagittal (dural) sinus* to the occipital region. From there, it flows to the *transverse (lateral)* and *sigmoid sinuses* into the *internal jugular vein*. All dural sinuses receive blood from veins in the immediate vicinity.

The deep cerebral drainage is to the region of the *foramina of Monro,* where the paired internal cerebral veins (posterior to the choroid plexus of the third ventricle) extend to the region of the pineal body. There, they join to form the *great vein of Galen*. Blood then flows, successively, through the *straight sinus* (located along the midline within the tentorium, which is dura mater lying between the cerebellum and occipital lobe), *transverse sinus*, and *sigmoid sinus* before draining into the *internal jugular vein* (**Figs. 4.4 and 5.1**). The straight sinus also receives venous blood from the inferior sagittal sinus located along the inferior margin of the falx cerebri just above the corpus callosum.

Some blood from the base of the cerebrum drains into the *superior* and *inferior petrosal sinuses* and then flows into either the *sigmoid sinus* or the *cavernous sinus* in the region of the hypothalamus (on the sides of the sphenoid bone). The cavernous sinus is connected via the superior petrosal sinus with the transverse sinus, via the inferior petrosal sinus with the jugular vein, and via the basilar venous plexus with the venous plexus of the vertebral canal (**Fig. 4.4**).

Emissary Veins

Some dural sinuses connect with the veins superficial to the skull by *emissary veins*. These veins act as pressure valves when intracranial pressure is raised and are also routes for spread of infection into the brain case (infection in the nose could spread via an emissary vein high in the nose into the meninges and could result in meningitis). The cavernous sinus is connected with emissary veins, including the ophthalmic vein, which extends into the orbit.

FUNCTIONAL CONSIDERATIONS

The mean blood flow in the normal brain is 50 mL/100 g of brain tissue per minute. It takes about 7 seconds for a drop of blood to flow through the brain. At any given moment, however, the flow through a specific region could be greater, the same, or less than the mean flow through the CNS. The brain is similar to other tissues of the body where the amount of blood flow varies with the level of metabolic and functional activity. For example, dynamic voluntary movements of the hand are associated with an increase in the blood flow within the

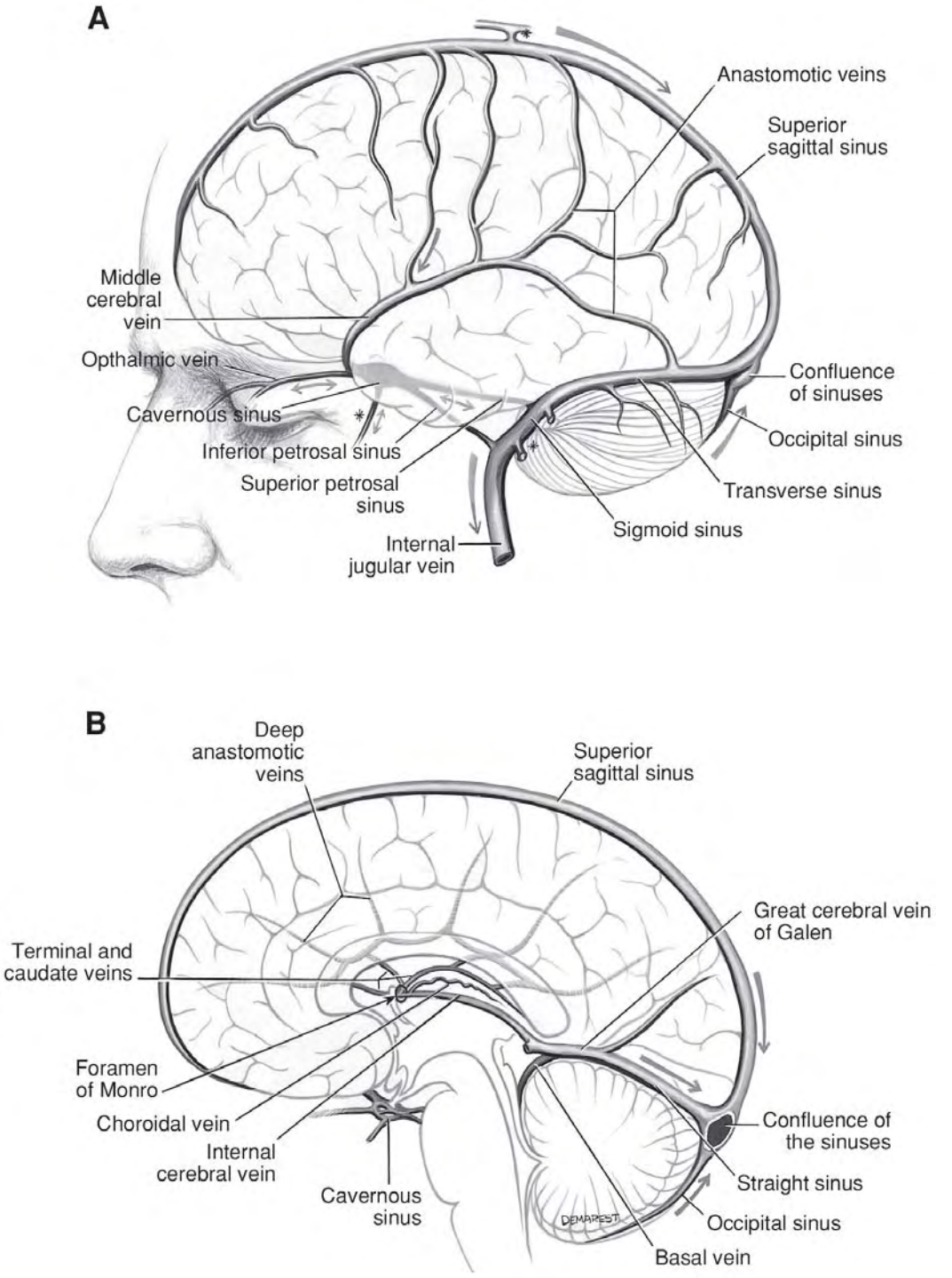


Figure 4.4: Venous drainage from the brain. **(A)** lateral view of the brain (*Location of emissary veins); **(B)** medial view of the brain.

cerebral cortical motor areas associated with hand movements and with sensory areas receiving signals from skin, joints, and muscles associated with these movements (Chap. 25).

Anastomotic connections within the vertebral and internal carotid arterial systems form extensive patterns of collateral circulation in the brain. A sudden deprivation of the blood supply to a region of the brain could, if the vascular insufficiency lasts for more than a few minutes, result in the necrosis (infarct) of brain tissue. The inadequate oxygen and glucose supply at the lesion (*infarct*) site is the essential cause of a "stroke" (sudden appearance of focal neurologic deficits). This could result from the sudden occlusion by a *thrombus* (blood clot formed within the blood vessel), or an *embolism* (a portion of clot transported along in the blood stream) to the occlusion site, or the rupture of an artery often the result of arteriosclerosis or hypertension; this is called a *cerebrovascular accident (CVA)*. A stroke is often preceded by a significant warning sign known as a *ministroke* or *transient ischemic attack (TIA)*. These temporary spells are the result of impaired neural function caused by a brief but definite reduction in blood flow to the brain. Depending on the location that is deprived of oxygen and glucose, the symptoms might include difficulty in talking, temporary weakness or paralysis on one side, dizziness, blurred vision, loss of hearing, and so forth.

Interconnections among the large branches of the superficial arteries are usually physiologically effective, so that an occlusion of one need not result in a marked impairment of the blood supply to the neural tissues. For example, following an occlusion within the circle of Willis, or its proximal branches, the collateral circulation is often adequate, especially if the involved artery becomes occluded slowly before the stroke. In contrast, anastomoses among the distal arterial branches of the circle of Willis are variable; consequently, the collateral circulation might not be adequate and occlusion of a vessel might result in an infarct. Rich anastomoses exist among the capillary beds of adjacent arteries within the substance of the brain, but an occlusion of the supplying arteries is often followed by neural damage, causing symptoms and signs correlated with the site (Chaps. 17 and 25). This occurs because the anastomotic connections are not sufficiently rich to allow adequate blood flow to reach the deprived areas rapidly enough to meet the high metabolic requirements.

An occlusion of the *anterior cerebral artery* results in a lesion of the paracentral lobule that has the general sensory and motor cortical areas for the contralateral lower extremity (Chap. 25). A lesion in this area results in contralateral paresis as a motor sign coupled with diminished sensitivity (hypoaesthesia) of the general senses in this extremity (Chap. 12). Blockage of the *calcarine branch of the posterior cerebral artery* (which supplies the primary visual cortex of one side) results in a contralateral hemianopsia (Chap. 19). Occlusion of small branches of the *posterior cerebral artery* (which supplies the posterior thalamus and adjacent tissues) produces the *thalamic syndrome* (Chap. 23). Strokes following the rupture and bleeding of the *striate arteries*, branches of the *middle cerebral artery* (which supply portions of the internal capsule and adjacent structures), result in signs that include an upper motoneuron paralysis of the face and upper and lower limbs on the opposite side as well as sensory disturbances (Chaps. 12 and 25). Signs associated with vascular lesions of branches of the *vertebral artery* supplying the brain stem are outlined in Chapter 17.

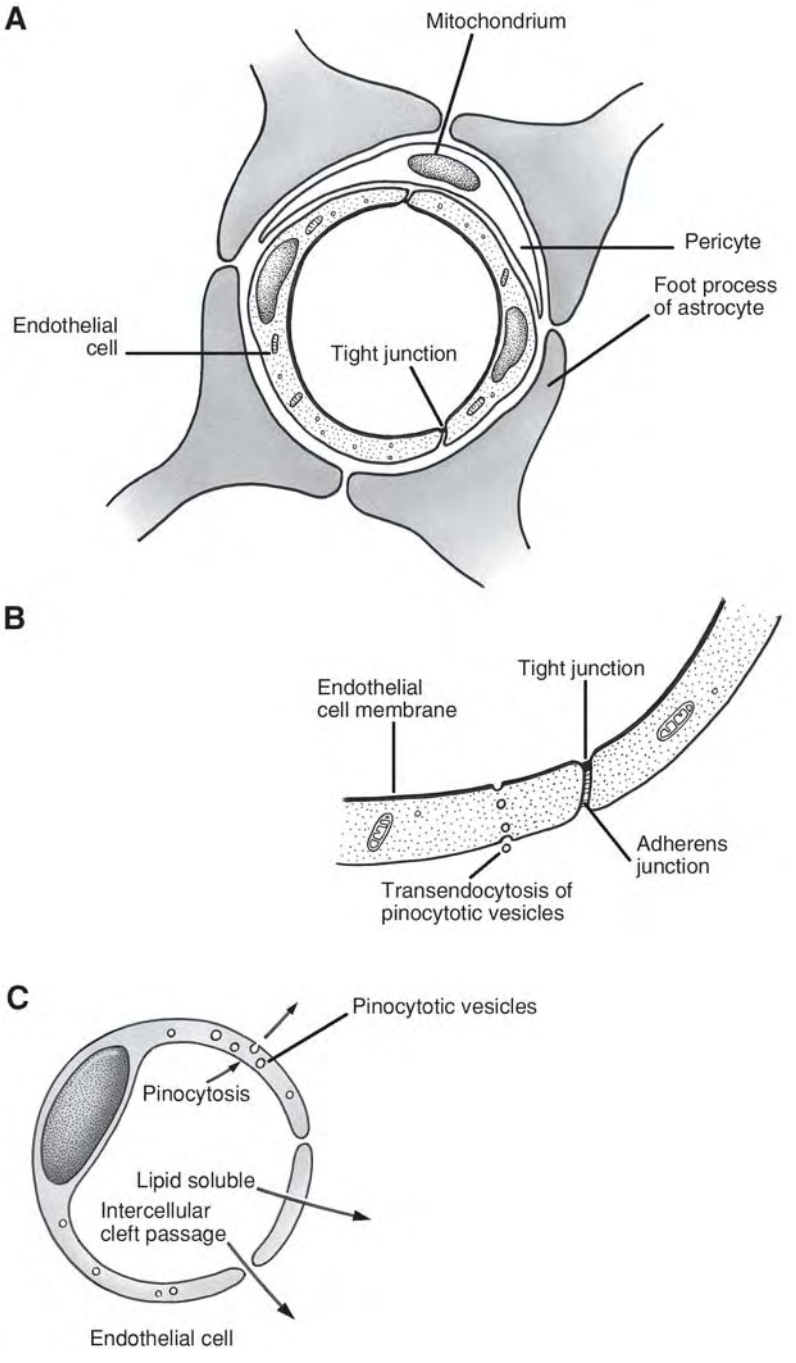
Although collateral circulation provides certain regions of the CNS with a margin of safety during arterial occlusion, the anastomotic network also allows for a degree of vulnerability. With a reduction in the systemic blood pressure, a region supplied by an anastomotic network is susceptible to ischemia; such an anastomosis occurs at the terminal ends of two or more arterial trees, a border region where perfusion pressure is lowest. These border regions, which are supplied by major arteries, are called *border zones* or *watershed zones*. An infarction occurring in such a region is called a *border zone* or *watershed zone infarct*.

BLOOD–BRAIN BARRIER

The *blood–brain barrier* (BBB) is a specialized functionally dynamic structure that maintains the microenvironment, thus enabling neurons to function effectively. Anatomically, the barrier consists of endothelial cells of the brain capillaries and their tight junctions (**Fig. 4.5**). The BBB's role is accomplished by activities that regulate the movement of various metabolites and other chemical substances between the blood and the brain by (1) exclusion, (2) selective passage, and/or (3) removal. The capillary bed is comprised of *endothelial cells* with adjacent smooth-muscle-like *pericytes* and *end-feet of astrocytes* that ensheathe the endothelial cells (**Fig. 4.5**). The contractile property of endothelial cells and the pericytes can alter the shape and size of a capillary lumen. *Exclusion* of blood-borne substances is largely regulated by the properties of the cell membrane of the brain's endothelial cells. For example, this membrane limits the passive diffusion of H_2O and certain aqueous substances from the blood. *Selective passage* of metabolites and chemical substances essential for the growth and function of the brain are conveyed (1) by the diffusion of some lipid-soluble substances by ion channels and transport proteins (transporters) and (2) by facilitative and energy-dependent receptors that mediate the transport of water-soluble substances. These include the transport from blood to brain of amino acids, peptides, and the energy substrate glucose. Removal of metabolites that accumulate in excess is conveyed by transporters from brain to blood (**Fig. 4.5**).

The combination of the specialized cell membrane of the endothelial cells linked by intercellular tight junctions is the hallmark of the BBB (**Fig. 4.5**). This duo effectively excludes by blocking the passage of many substances across the capillary wall. The permeability property can be enhanced by the state of phosphorylation of the proteins of the cell–cell adherens junctions. The cadherin proteins of the adherens junctions also act as a signaling component between endothelial cells through linkages with the cytoskeletal protein filaments of the endothelial cells. The presence of so few pinocytotic vesicles within the endothelial cells is indicative that the transcellular movement by vesicles across the BBB (transendocytosis) is both relatively deficient and slow. However, the selective passage of substances is related to the presence of high concentrations of carrier-mediated transport systems that act as transporters for glucose, essential amino acids, other required nutrients, and macromolecules. These ensure the passage of essential substances from the blood to the CNS. The perivascular astrocytes with end-feet that ensheathe about 95% of the capillary surface are not considered to be a component of the BBB. Some evidence suggests that the early proliferating perineural blood vessels, composed of primordial fenestrated endothelial cells with no BBB, might be induced by brain-derived molecular signals from early perivascular astroglia to develop into endothelial cells lacking fenestrations and, thus, express BBB properties.

Figure 4.5: Ultrastructural features of the specialized capillary endothelial cells of the brain compared to a general capillary. **A,B:** *Brain capillary.* The endothelial cells (ECs) have several anatomic features that contribute to the so-called blood–brain barrier (BBB). Transcellular passage of substances across the BBB from the blood to brain is regulated, in part, by the combination of restrictions, including specialized cell membranes of the ECs adjacent to the bloodstream, tight junctions between ECs, a scarcity of pinocytotic vesicles, and selective transport of water-soluble compounds by transendocytosis. The presence of abundant mitochondria supplies the energy-dependent transport system delivering substances required by the brain. The cell-to-cell adherens junctions contribute minimally to the BBB. The foot processes of the astrocytes that almost completely ensheath the brain capillaries are not functional components of the BBB, but could influence "barrier-specific endothelial cell differentiation." Note the smooth muscle-like pericyte



adjacent to the capillary. **C:** *General (systemic) capillary.* In contrast, the relatively unselective diffusion across endothelial cells of other organs is enhanced by the presence of fenestra, interendothelial cleft passage of fluid, numerous pinocytotic vesicles, and few mitochondria and the absence of tight junctions.

The selective passage of essential substances that must cross the BBB in sufficient quantities is primarily accomplished by the diffusion of lipid-soluble solutes and by facilitative and carrier-mediated transport of water-soluble substances. The great concentrations of mitochondria within the endothelial cells are indicative of high oxidative metabolic activity required by the carrier-mediated transport systems. This explains, in part, why small molecules pass through the barrier more rapidly than medium-sized molecules and why large molecules such as serum proteins and penicillin do not pass through the BBB.

Diffusion

Lipid-soluble solutes such as O_2, CO_2, and some drugs pass rapidly from the blood through the barrier into the brain. Facilitated diffusion occurs "downhill" down a concentration gradient because it is not energy dependent. Systems that move molecules rapidly without consuming energy act bidirectionally from the brain and cerebrospinal fluid to blood and vice versa, thereby influencing the passage to and from blood plasma and brain.

Carrier-Mediated Transport Systems

Most substances that must cross the BBB are not lipid soluble. They cross by facilitated diffusion and energy-dependent carrier-mediated active transporters (membrane-spanning proteins that facilitate the passage of small molecules), which are the conveyers of the numerous essential water-soluble substances such as glucose, amino acids, lactate, ribonucleosides, and several vitamins that cross the BBB. In these forms of transport, the solute (e.g., 99% of the glucose) combines with a specific membrane carrier on one side of the barrier and then "shuttles" the solute across the barrier for release. These systems are efficient for transporting the glucose and other critical nutrients that must be supplied continuously and in a large quantity. Should the brain be inadequately supplied with sufficient glucose or oxygen, loss of consciousness and even death can occur within minutes.

An astrocyte might have processes with several end-feet that come in close contact with a capillary, with a neuron, and with the pia–glial membrane (**Fig. 5.5**). Thus, an astrocyte might have a transport function of transferring metabolites bidirectionally among the endothelial cells, neurons, and cerebrospinal fluid. . Astrocytes can (1) take up from the extracellular fluid the excess potassium ions generated during intense neuronal activity and (2) regulate the extraneural concentrations of neurotransmitters by an uptake process and store them.

Activated lymphocytes, macrophages, and certain types of metastatic cell can cross the BBB barrier. These cells can recognize and bind to endothelial cells and then activate signaling systems that initiate transmigration junctional-opening mechanisms. Another permeability barrier, called the *blood–cerebrospinal fluid barrier,* is present between the capillaries of the choroid plexus and the cerebrospinal fluid (Chap. 5).

The ependymal cells and subjacent astrocytes (i.e., subependymal glial membrane) of the ventricles constitute a brain–cerebrospinal fluid interface (**Fig. 5.6**). The lateral cell surfaces of the ependymal cells are comparatively simple without elaborate folds or interdigitations. This structural arrangement forms the brain-cerebrospinal fluid interface. Neither the ependymal surfaces of the ventricles nor the pia–glial membrane on the surface of the brain impede the exchanges of substances of between the cerebrospinal fluid and the capillaries of the brain. Thus, the brain–cerebrospinal fluid interface does not constitute a BBB.

Homeostasis of the neuronal environment is vital for the proper functioning of each neuron. In turn, barriers are essential for the preservation of *homeostasis* by maintaining the ionic constancy of the extraneuronal interstitial fluid (fluid surrounding the neurons, glial cells, and capillaries) by promoting the entry of required molecules, by preventing the entry of unwanted substances. and by removing unwanted substances. Following infections, stroke, tumors, or trauma, the blood–brain barrier can be breached.

SUGGESTED READINGS

Bevan RD, Bevan JA. *The Human Brain Circulation: Cunctional Changes in Disease.* Totowa, NJ: Humana; 1994.

Brightman M. Implication of astroglia in the blood-brain barrier. *Ann. NY Acad. Sci.* 1991;633: 343–347.

Brightman MW, Kadota Y. Nonpermeable and permeable vessels of the brain. *NIDA Res. Monogr.* 1992;120:87–107.

Brightman MW, Ishihara S, Chang L. Penetration of solutes, viruses, and cells across the blood-brain barrier. *Curr. Topics Microbiol. Immunol.* 1995;202:63–78.

Brust J. Circulation of the brain. In: Kandel WR, Schwartz JH, Jessel T., eds. *Principles of Neural Science,* 4th ed. New York: McGraw-Hill, 2002; 1303–1316.

Cassella JP, Lawrenson JG, Firth JA. Development of endothelial paracellular clefts and their tight junctions in the pial microvessels of the rat. *J. Neurocytol.* 1997;26:567–575.

Cassella JP, Lawrenson JG, Allt G, Firth JA. Ontogeny of four blood–brain barrier markers: an immunocytochemical comparison of pial and cerebral cortical microvessels. *J. Anat.* 1996;189(Pt 2):407–415.

Cucullo L, McAllister MS, Kight K, et al. A new dynamic in vitro model for the multidimensional study of astrocyte-endothelial cell interactions at the blood–brain barrier. *Brain Res.* 2002;951: 243–254.

Harik SI, Kalaria RN. Blood–brain barrier abnormalities in Alzheimer's disease. *Ann. NY Acad. Sci.* 1991;640:47–52.

Harik SI, Gravina SA, Kalaria RN. Glucose transporter of the blood–brain barrier and brain in chronic hyperglycemia. *J. Neurochem.* 1988;51: 1930–1934.

Isobe I, Watanabe T, Yotsuyanagi T, et al. Astrocytic contributions to blood–brain barrier (BBB) formation by endothelial cells: a possible use of aortic endothelial cell for in vitro BBB model. *Neurochem Int.* 1996;28:523–533.

McAllister MS, Krizanac-Bengez L, Macchia F, et al. Mechanisms of glucose transport at the blood–brain barrier: an in vitro study. *Brain Res.* 2001; 904:20–30.

Pardridge W. The Blood–Brain-Barrier. *Cellular and Molecular Biology.* New York, NY: Raven Press; 1993.

Pardridge WM. Blood–brain barrier genomics and the use of endogenous transporters to cause drug penetration into the brain. *Curr. Opin. Drug Discov. Dev.* 2003;6:683–691.

Pardridge WM. Molecular biology of the blood–brain barrier. *Methods Mol. Med.* 2003;89: 385–399.

Purves MJ. *The Physiology of the Cerebral Circulation.* Monographs of the Physiological Society No. 28. Cambridge: Cambridge University Press; 1972.

Reese TS, Feder N, Brightman MW. Electron microscopic study of the blood–brain and blood–cerebrospinal fluid barriers with microperoxidase. *J. Neuropathol. Exp. Neurol.* 1971;30: 137–138.

Rubin LL, Staddon JM. The cell biology of the blood–brain barrier. *Annu. Rev. Neurosci.* 1999;22:11–28.

Stanness KA, Westrum LE, Fornaciari E, et al. Morphological and functional characterization of an in vitro blood–brain barrier model. *Brain Res.* 1997;771:329–342.

Tao-Cheng JH, Nagy Z, Brightman MW. Tight junctions of brain endothelium in vitro are enhanced by astroglia. *J. Neurosci.* 1987;7:3293–3299.

Walz W. *The Neuronal Environment: Brain Homeostasis in Health and Disease.* Totowa, NJ: Humana, 2002.

5
Meninges, Ventricles and Cerebrospinal Fluid

Meninges
Ventricles
Fluid Environment of the Brain
Circumventricular (Periventricular) Organs
Hydrocephalus
Clinical Aspects of Cerebrospinal Fluid

The meninges are three layers of connective tissue that surround and protect the soft brain and spinal cord. Cerebrospinal fluid (CSF) passes between two of the layers of the meninges and, thus, slowly circulates over the entire perimeter of the central nervous system (CNS). CSF also flows through the ventricles, which are the cavities within the brain derived from the central canal of the embryonic neural tube (**Fig. 5.1**).

MENINGES

Each of the meningeal layers—pia mater, arachnoid and dura mater—is a separate, continuous sheet: thin strands of connective tissue called *trabeculae* extend from the arachnoid to the pia mater (**Fig. 5.2**).

The *pia mater* is intimately attached to the brain and spinal cord, dipping into every sulcus and fissure. It is a vascular layer containing blood vessels whose branches nourish the underlying neural tissue.

The *arachnoid* is a thin, avascular, delicate layer, which does not follow each indentation of the brain, but, rather, skips from crest to crest. The *subarachnoid space*, between the pia mater and the arachnoid, contains CSF and large blood vessels. In several places, the subarachnoid space is enlarged into *cisterns*. The *cisterna magna (cerebellomedullary cistern)* is located dorsal to the medulla and inferior to the cerebellum. The *pontine* and *interpeduncular cisterns* are located on the anterior brainstem, and the *superior cistern* is located posterior to the midbrain. The *spinal (lumbar) cistern* is located caudal to the spinal cord (lumbar-2 to sacral-2 vertebral levels). Large cisterns at the base of the brain are traversed by arteries.

In the head, the tough nonstretchable *dura mater* consists of two layers: the *outer and inner dura mater*. The skull and dura mater form an inelastic envelope enclosing the CNS, CSF, and blood vessels. This inelasticity permits only a slight increase in the cranial contents; the concept that the volume of the intracranial contents cannot change is the basis of the Monro–Kellie doctrine (*see* "CSF Pressure"). The *outer dura mater* is really the periosteum of the skull. The *inner dura mater* is a thick membrane, which extends (1) between the two cerebral hemispheres in the midsagittal plane as the *falx cerebri* and (2) between the occipital lobes and the cerebellum as the *tentorium cerebelli*. The *subdural space* is a potential thin space located between the inner dura mater and the arachnoid. The film of fluid in the subdural space is not CSF.

The dura mater is also called the *pachymeninx* and the arachnoid and pia mater comprise the *leptomeninges*.

In head injuries, bleeding could occur into the subarachnoid space (*subarachnoid hemorrhage*), into the subdural space (*subdural hemorrhage*), and between the outer dura mater and

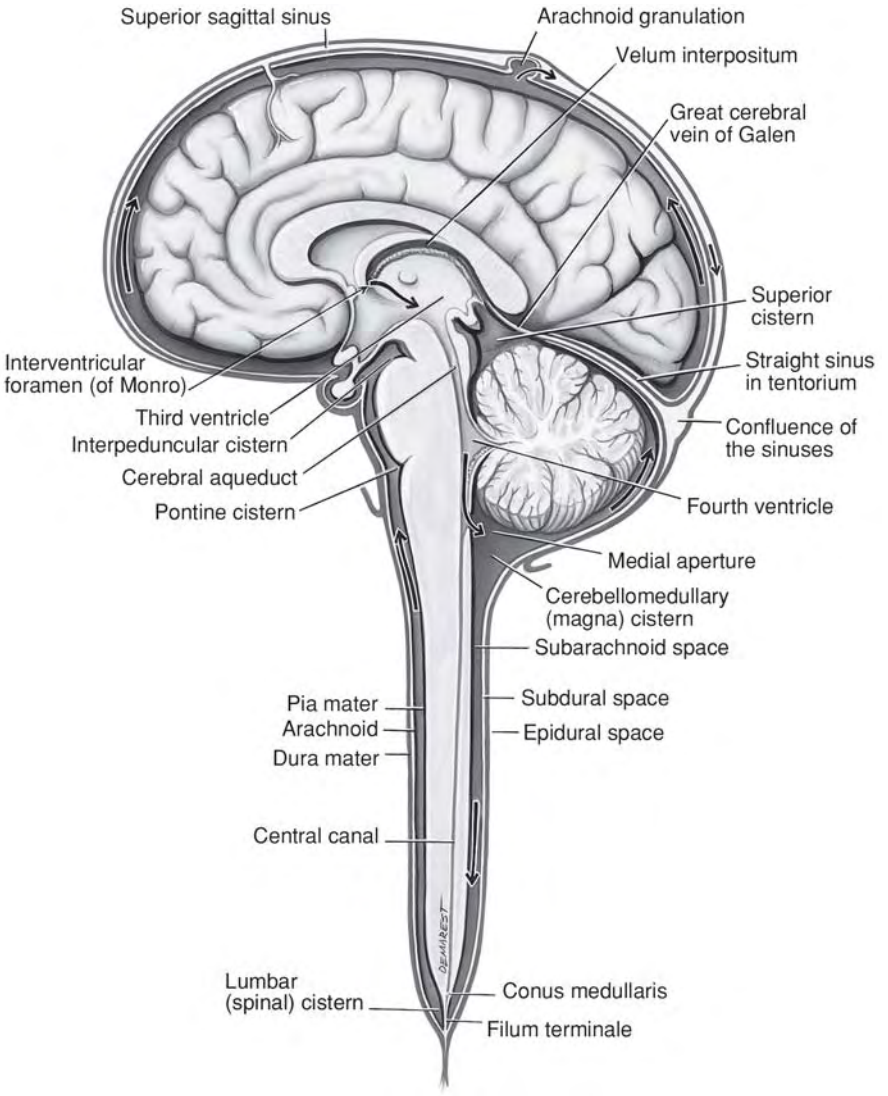


Figure 5.1: Midsagittal view of the meninges, ventricles, subarachnoid spaces, and cisternae. Arrows indicate the normal direction of CSF flow.

the skull (*extradural hemorrhage*). An extradural hemorrhage could result from the bleeding of meningeal vessels after a fracture of the skull. A subdural hemorrhage could be caused by the tearing of veins crossing the subdural space, which might follow after the sudden movement of the cerebral hemispheres relative to the dura and skull. A subarachnoid hemorrhage could result from the rupture of an aneurysm; bloody CSF obtained from a lumbar puncture is confirmatory.

VENTRICLES

The *ventricular system* is a series of cavities within the brain, lined by ependyma and filled with CSF. The ependyma is a simple cuboidal

epithelial layer of glial cells. Paired *lateral ventricles*, within the substance of the cerebral hemispheres, communicate with the midline *third ventricle* via the *interventricular foramina of Monro* (**Figs. 5.3 and 5.4**). The third ventricle is continuous with the tubelike *cerebral aqueduct of Sylvius* (*iter*) in the midbrain, and the latter with the *fourth ventricle* in the pons and medulla (**Fig. 5.1**). The fourth ventricle, in turn, is continuous with the *central canal* that extends from the caudal medulla almost to the lower tip of the spinal cord, where it terminates without outlet. The central canal has a small diameter and is, for the most part, occluded. Each lateral ventricle is subdivided into four parts: *anterior horn* in the frontal lobe (rostral to foramen of Monro), *body* in the parietal lobe, *inferior horn* in the temporal lobe, and *posterior horn* in the occipital lobe.

Each ventricle contains a *choroid plexus*, a rich network of blood vessels of the pia mater that is intimately related to the ependymal lining of the ventricles. The membrane formed by the pia mater, its vascular network, connective tissue, and ependyma is called the *tela choroidea*. The choroid plexus of each lateral ventricle is located in the body and inferior horn; it is continuous through the foramen of Monro with the unpaired choroid plexus of the roof of the third ventricle (**Fig. 5.3**). The choroid plexus of the fourth ventricle is located in the roof of the medulla, in which there are three foramina through which CSF escapes from the fourth ventricle into the cisterna magna. The two lateral openings are the *lateral*

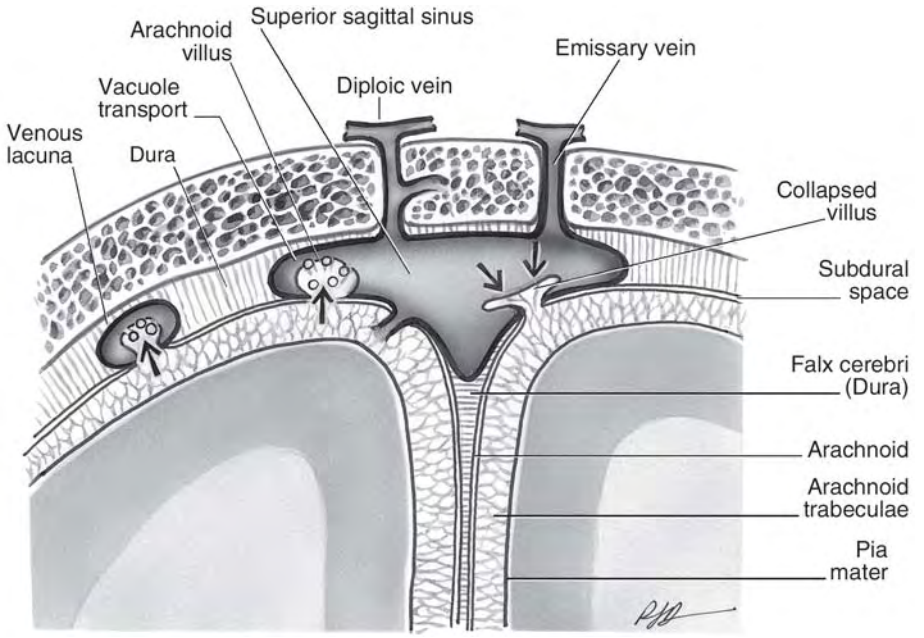


Figure 5.2: Coronal section through the superior sagittal sinus and associated structures. Vacuole transport within the villi of the arachnoid granulations (arrows on left side of midline) appears to occur via one-way bulk-flow of CSF via giant vacuoles from the subarachnoid space into the venous blood of the dural sinus. The collapsed villus lacking vacuoles (on the right side) is indicative of a markedly reduced bulk flow of CSF via vacuoles. The one-way flow is called bulk flow within each villus because all constituents of the CSF, including small molecules, micro-organisms, and even erythrocytes, are transported with the vacuoles. The dura mater represents the combined inner dura mater and outer dura mater.

apertures (*foramina of Luschka*) and the medial opening is the *medial aperture* (*foramen of Magendie*) (**Fig. 5.4**).

FLUID ENVIRONMENT OF THE BRAIN

The brain and spinal cord can only function in a chemically stable homeostatic fluid environment. This comprises (1) the interstitial fluid bathing the neurons, glia, and blood vessels within the central nervous system and (2) the CSF. These two fluids are essentially similar in composition.

The extracellular fluid occupies a space of about 15–20% of the volume of the brain. This interstitial space is greater in the gray matter than in the white matter. The former has higher water content than the latter. This fluid joins the choroid plexus-produced CSF within the subarachnoid space. This CSF is constantly being renewed by production and resorption so that the total volume is replaced several times a day.

Two structures have critical roles in the formation and maintenance of this environment: (1) the brain capillaries and (2) choroid plexuses. They act as selective barriers and major transfer sites of certain substances that constitute these fluids.

Tight junctions between endothelial cells of the cerebral capillaries form the so-called blood–brain barrier between the blood and the interstitial fluid. The capillaries and the ependymal epithelial cells of the choroid plexus form the blood–cerebrospinal fluid barrier between the blood and CSF (**Figs. 5.5 and 5.6**). In addition, the arachnoid is essentially impermeable to water-soluble substances and its role is largely passive.

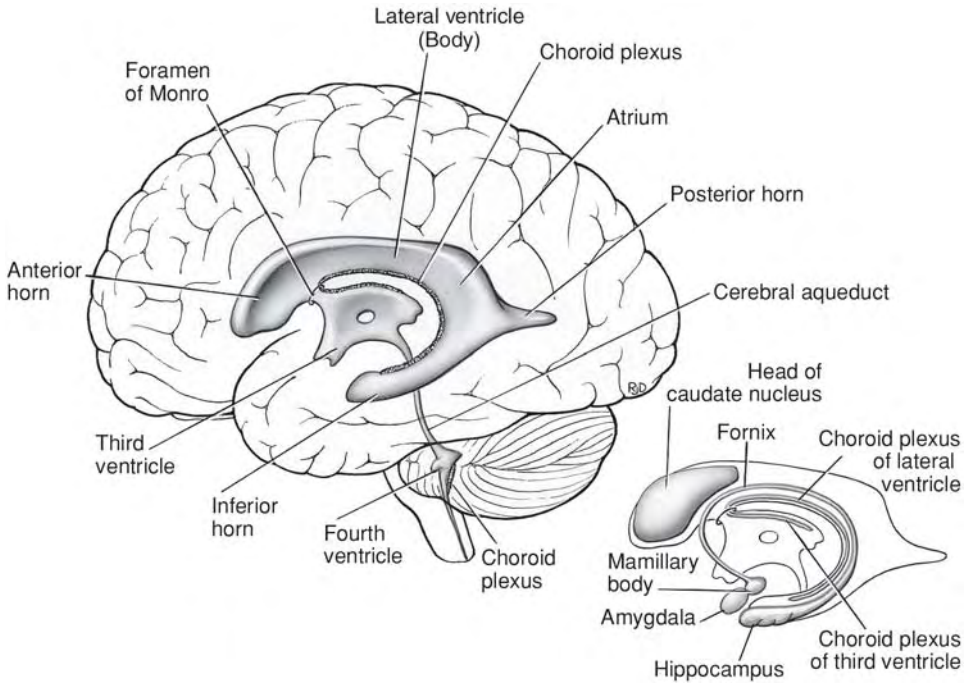


Figure 5.3: Lateral view of the ventricles of the brain. Note in the small drawing that the choroid plexus of the lateral ventricle, the hippocampus–fornix complex, and the caudate nucleus parallel the curvature of the lateral ventricle. The caudate nucleus is cut off just behind its head in this view.

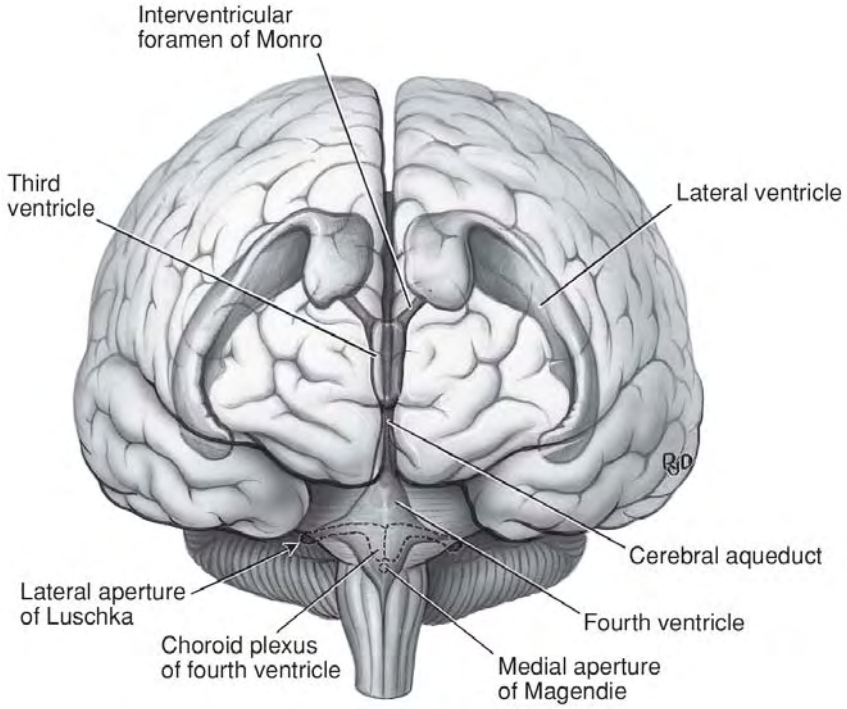


Figure 5.4: Frontal **(A)** and lateral **(B)** views of the ventricles of the brain.

Cerebrospinal Fluid

Cerebrospinal fluid is a crystal clear, colorless solution that looks like water and is found in the ventricular system and the subarachnoid space. It consists of water, small amounts of protein, gases in solution (oxygen and carbon dioxide), sodium, potassium, magnesium, and chloride ions, glucose, and a few white cells (mostly lymphocytes).

The CSF, formed primarily by a combination of capillary filtration and active epithelial secretion, serves two major functional roles:

1. *Physical Support*. By acting as a "water jacket" surrounding the brain and by providing buoyancy for it, the CSF protects, supports, and keeps the brain afloat in a sea of fluid.
2. *Homeostasis*. The CSF of the ventricles and the subarachnoid space comprises a pool to which some of the endogenous water-soluble products, including unwanted substances, drain by diffusion from extracellular fluids of the brain to the ventricles and subarachnoid space. Other products of brain metabolism are removed to the blood flowing through the capillaries. The CSF and capillaries act as substitutes for the lack of a lymphatic system in the brain and spinal cord. The CSF along with extracellular fluids surrounding the neurons are the "expressions" of state of chemical equilibrium of the neural environment, called *homeostasis*, essential for the normal functioning of the central nervous system.

The brain and spinal cord actually float in the CSF; the 1400-g brain has a net weight of about 25 g while suspended in the CSF (reduces brain weight 60-fold). The brain is "shock mounted" in the CSF and, thus, is able to withstand the stress during sudden movements of the head. Illustrative of its buoyancy, removal of the CSF as was done in pneumoen-

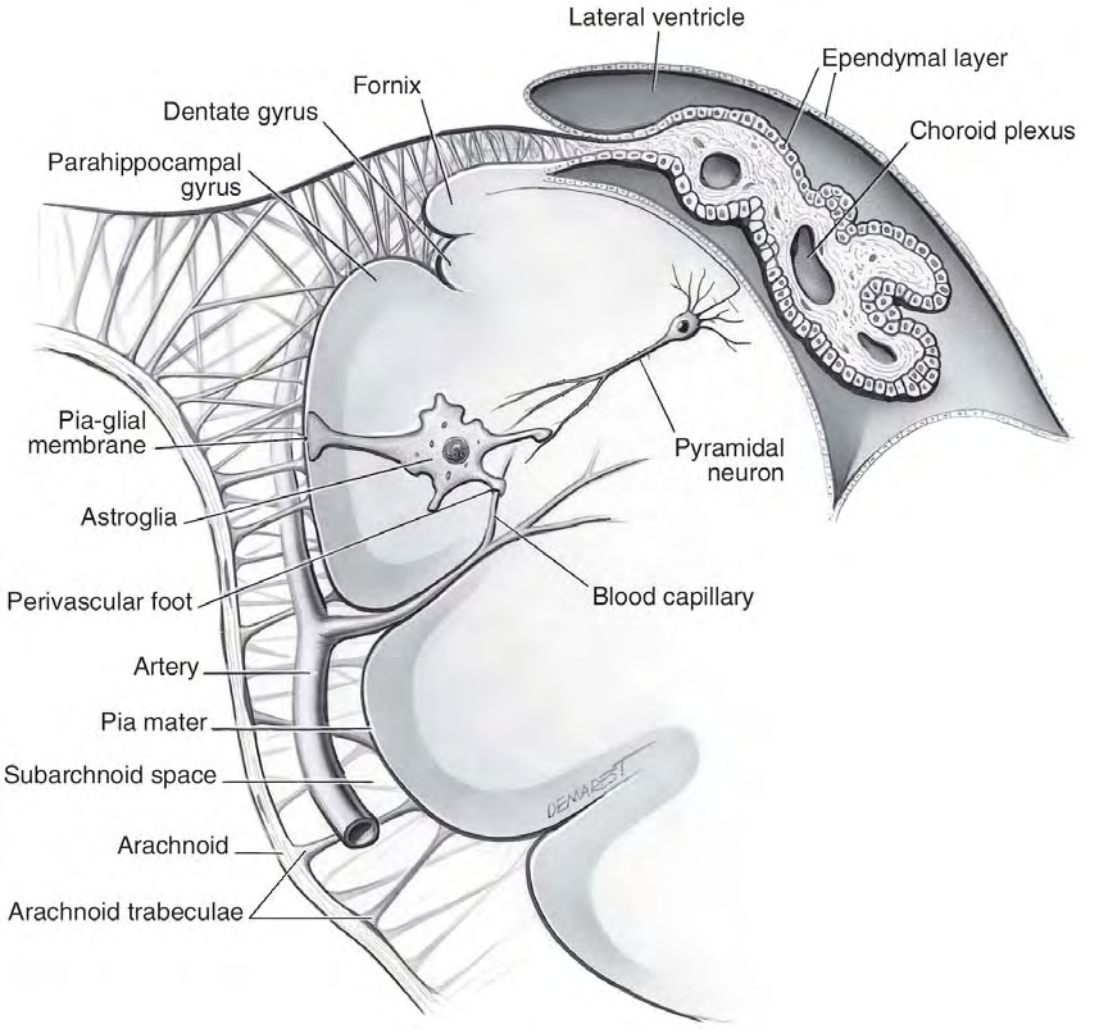


Figure 5.5: Relations of the leptomeninges, subarachnoid, choroid plexus, ventricle, astroglia, and neurons of the CNS. The subarachnoid space is located between the arachnoid and pia mater. The choroid plexus is composed of an ependymal layer and a highly vascularized connective tissue core. Subarachnoid blood vessels and subarachnoid space are continuous with the core of the choroid plexus. The astrocyte has several processes: One extends to a blood capillary and terminates as a perivascular foot, another process extends to and contacts the pyramidal neuron, and another extends to the pia mater. The pia mater and arachnoid constitute the leptomeninges. The dura mater is called the pachymeninx.

cephalography caused intense pain and headaches with each movement of the head, which persisted until the fluid was naturally replenished.

The headaches were attributed to irritation of nerve endings in the meninges and intracranial blood vessels. Headaches rarely occur when a small sample of CSF is removed for chemical analysis. The volume of CSF in an adult is about 150 mL (60 mL in the ventricles and 90 mL in the subarachnoid space, including the lumbar cistern; Chap. 7). CSF is formed

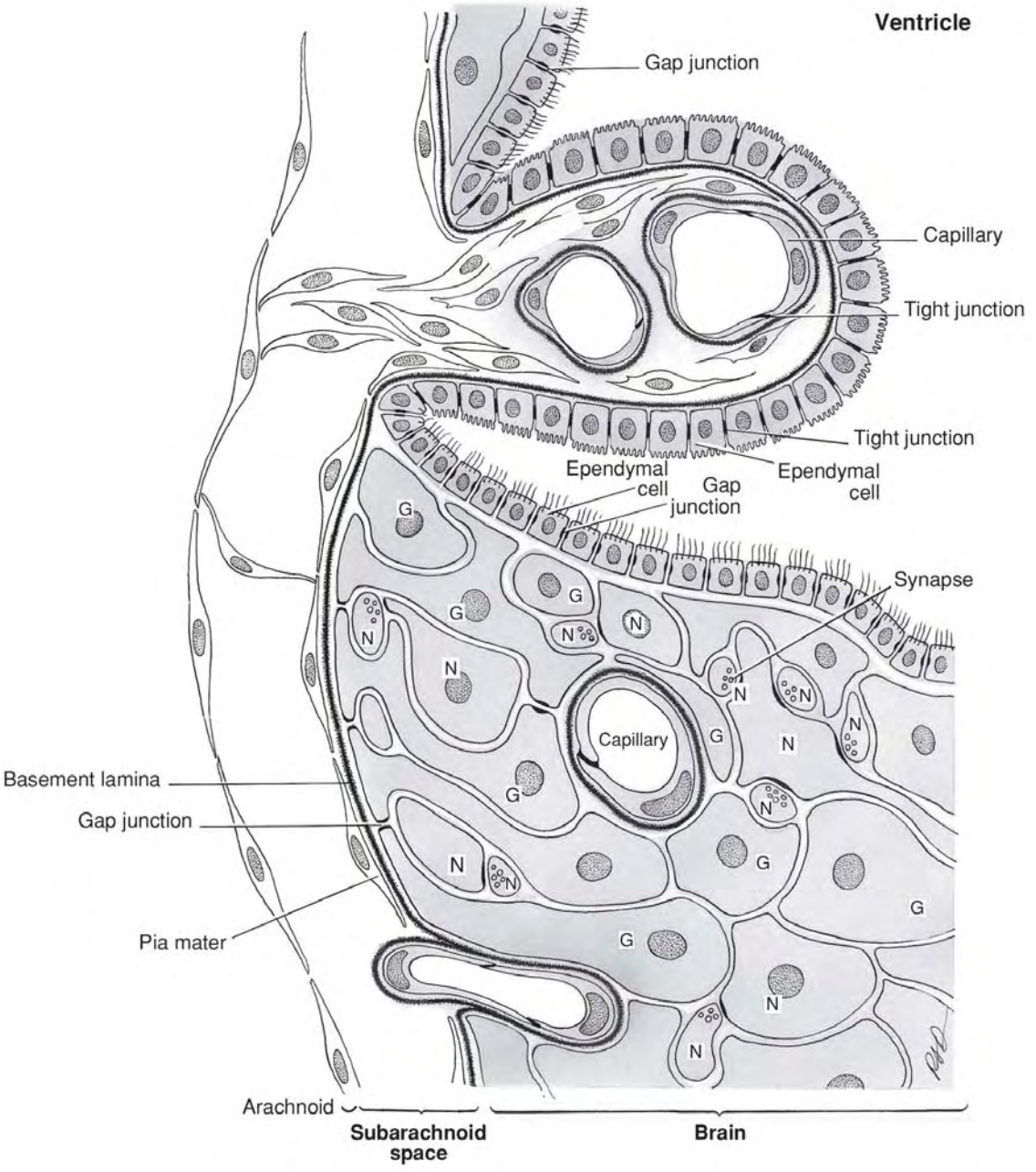


Figure 5.6: Ultrastructural features in the brain, choroid plexus, pia– arachnoid layer, and ventricle. The continuous extracellular space is located among the glia (G), neurons or their processes (N), and the capillary. The basement lamina (also surrounds the capillary) is a porous structure. Note the tight junctions between capillary endothelial cells and choroid plexus ependymal cells, and the gap junctions between pial cells and ependymal cells lining the ventricle.

at a rate of approximately 500 mL/day; that is, the total volume is replaced every 3-4 hours.

The interstitial fluid within the brain is readily exchanged with CSF. As the CSF flows through the ventricles and the subarachnoid space around the spinal cord and brain, the exchange between the two fluids occurs (1) at the leaky spaces (gap junctions; **Fig. 5.6**) of the ependymal layer within the ventricles and (2) at the perivascular spaces on the pial surface of the CNS.

Choroid Plexus and the Blood–Cerebrospinal Fluid Barrier

The choroid plexus comprises a single row of choroidal epithelium, arranged as villi around a core of blood vessels derived from the pia mater and connective tissue **Figs. 5.5 and 5.6**). The choroidal epithelium is continuous with the ependyma of the ventricles. The extensive vascular network of the plexus is an expression of its active metabolic activity. The ventricular surface of each choroidal cell has a brush border comprised of microvilli, a feature of epithelial cells noted for fluid transport. These cells contain many oxidative enzymes, which are indicative of their role in the active transport of electrolytes and other solutes. Tight junctions join adjacent endothelial cells of the brain and the choroid plexus, adjacent choroidal epithelial cells, and adjacent cells of the arachnoid membrane. These tight junctions are a barrier to the passage of macromolecules (1) from the blood to the ventricular CSF (CSF secretion) and (2) from the CSF to the capillary blood (absorption by the choroid plexus). The mechanism of CSF secretion and absorption from the CSF can be summarized as follows. The hydrostatic pressure within the choroidal capillaries initiates the passage of water and ions across the endothelial cells to the interstitial connective tissue and then to the choroidal epithelium. The completion of the transfer to the CSF takes two routes; (1) *transcellular movement* through the epithelial choroidal cells and across the plasma membrane into the ventricular cavity and (2) *paracellular movement* across the tight junction to the ventricular cavity. Both of these transfers are thought to be dependent on ion pumps. The details of the means for the transfer of molecules from the ventricular CSF to the capillaries have not been fully resolved.

The choroid plexuses of the four ventricles where the blood–cerebrospinal fluid barrier is located continuously secrete most of the CSF. Impermeable *tight junctions* join the endothelial cells and also the cuboidal ependymal cells of the choroid plexus (**Fig. 5.6**). These junctional barriers prevent the serum proteins from entering the CNS and inhibit the free diffusion of water-soluble molecules. The formation of the CSF by the choroid plexus involves capillary filtration and active transport by the ependymal cells. Flow of molecules across the cells of the choroid plexus occurs via active transport (energy required), facilitated diffusion (no energy required), and facilitated exchanges of ions (e.g., sodium, potassium, and chloride ions). Although the CSF is characterized as a cell-free, low-protein ultrafiltrate of blood and that the CSF and blood plasma are in osmotic equilibrium, some small but significant differences do exist between the two fluids. As compared to the blood plasma, CSF contains less potassium, bicarbonate, calcium, and glucose and more magnesium and chloride; its pH is lower.

The choroid plexus acts as a *"kidney" of the brain* that maintains the chemical stability of the CSF in a similar fashion as the kidney maintains the chemical stability of the blood. A key difference in this comparison is that the kidney removes waste products from the blood, whereas the choroid plexus pumps some "waste products" (byproducts of metabolic activity) from the CNS into the blood.

These barriers consist of permeability barriers that comprise systems whose primary roles are to preserve *homeostasis* in the central nervous system. They facilitate the entry of essential substances and metabolites and they block the entry or facilitate the removal of toxic substances and unnecessary metabolites. In many neurologic diseases, the blood–brain barrier breaks down and does not function as usual,

with some substances normally excluded passing through the barrier. This occurs in some infections, strokes, brain tumors, and trauma.

Flow of CSF

After its formation at the choroid plexuses and in the ventricular surfaces, there is bulk flow of CSF through the ventricular system, the subarachnoid spaces, and cisterns surrounding the CNS before it enters the systemic blood circulation. The CSF travels from the lateral ventricles through the foramina of Monro into the third ventricle, through the narrow cerebral aqueduct into the fourth ventricle, through the paired apertures of Luschka and the median aperture of Magendie within the tela choroidea in the roof of the fourth ventricle into the cisterna magna, and then slowly circulates rostrally through the subarachnoid space to the region of the superior sagittal venous sinus at the top of the skull (**Fig. 5.1**). Most of the CSF appears to enter the venous blood by a one-way *bulk flow* via vacuole (some of giant size) transport from the subarachnoid space through the cells of the *arachnoid villi* (pacchionian granulations) into the dural venous sinuses (**Fig. 5.2**). This one-way passage is called bulk flow because all constituents leave with the CSF including small molecules, micro-organisms, and even, at times, erythrocytes. These villi are grossly visible spongelike herniations of the arachnoid that penetrate into the lumen of the superior sagittal sinus. CSF also extends into and fills the tubular extensions of the arachnoid and subarachnoid space that form the sleeves around the roots of the spinal nerves (**Fig. 5.7**). These numerous microscopically visible arachnoid villi associated with spinal veins of the spinal roots absorb some CSF.

CSF Pressure

Cerebrospinal fluid pressure is lower than blood pressure. In an individual lying sideways, the pressure varies from 65 to 195 mm of

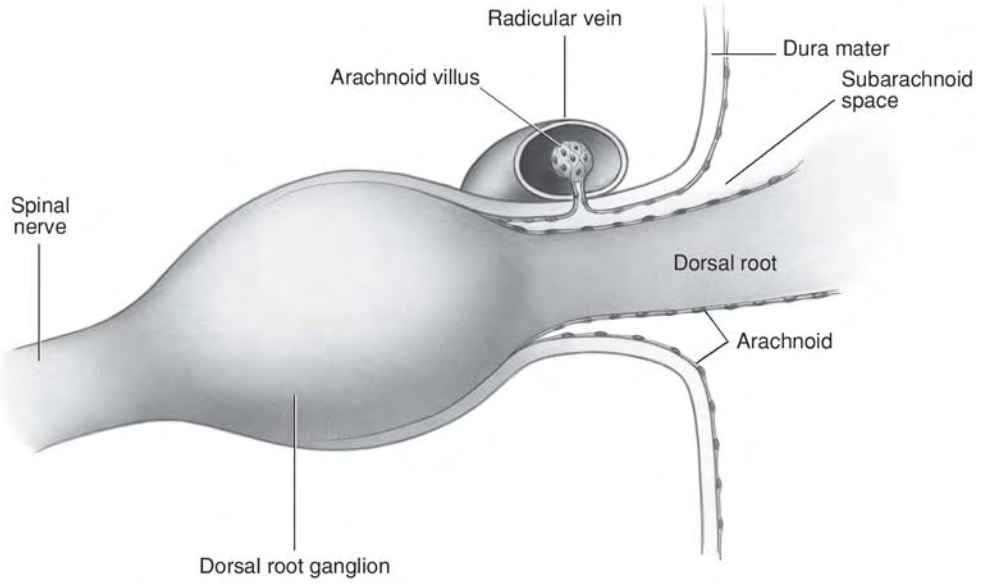


Figure 5.7: Dorsal view of a dorsal root ganglion and dorsal root illustrating an *arachnoid villus* adjacent to the dorsal root (spinal cord to the right of figure). The arachnoid, CSF, and subarachnoid space of the spinal canal extend as sleeves that surround the ganglion and roots of each spinal nerve. The arachnoid of this sleeve protrudes into a spinal root (radicular) vein to form an arachnoid villus from which some CSF can pass into a vein. (Adapted from Fishman., 1992)

water throughout the subarachnoid space. In a seated subject, the pressure may rise to between 200 and 300 mm of water in the lumbar cistern, reach zero in the cisterna magna, and go below atmospheric pressure in the ventricles. Fluctuations in the pressure occur in response to phases of the heartbeat and the respiratory cycle. These shifts occur because the rigid box of dura and skull does not yield, so that the intracranial pressure changes if additions or subtractions to the intracranial contents occur (*Monro–Kellie doctrine*).

An obstruction to the normal passage of CSF results in a backup of CSF and an increase in intracranial pressure. Because the CSF extends to the optic disk (optic nerve head, blind spot) of the subarachnoid space within the dural sleeve along the optic nerve, an elevated CSF pressure results in dilated retinal veins and forward thrust of the optic disk beyond the level of the retina. This *papilledema*, or so-called "*choked disk*", can be observed during an inspection of the fundus of the eye with an ophthalmoscope. A persistent papilledema could result in damaged optic nerve fibers.

CIRCUMVENTRICULAR (PERIVENTRICULAR) ORGANS

Adjacent to the median ventricular cavities (third ventricle, cerebral aqueduct, and fourth ventricle) are several specialized regions of ependymal origin called *circumventricular organs* (**Fig. 21.5**). The common vascular, ependymal, and neural organization of these structures differs from that found in typical brain tissue. They are referred to as "being in the brain, but not of it," in part because their capillaries are lined by fenestrated endothelial cells indicative of a defective blood–brain barrier to macromolecules. In humans, these anatomically well-defined organs include (1) the *median eminence of the tuber cinereum* (hypothalamus), the *neurohypophysis,* and the *pineal body*, all of which have a role in neuroendocrine regulation (Chap. 21), and (2) the *subcommissural organ, organum vasculosum of the lamina terminalis, subfornical organ,* and *area postrema* (Chap. 21). The functional roles of the latter group are largely unknown. The area postrema is a chemoreceptive structure activated by blood-borne substances that elicit vomiting and its removal causes refractoriness to some but not all forms of emetic stimuli.

HYDROCEPHALUS

An increase in the volume of CSF within the skull is known as hydrocephalus. Several types exist. In *compensating hydrocephalus*, there is no increase in pressure; this usually occurs when cerebral atrophy associated with a primary CNS disease is compensated with an increase in CSF volume. In *obstructive hydrocephalus* and *communicating hydrocephalus*, there is both an increase in volume and in pressure of the CSF. Obstructive hydrocephalus occurs when there is an obstruction to the flow of CSF within the ventricles, cerebral aqueduc,t or the apertures in the roof of the fourth ventricle. The blockage results in an increase in the volume of CSF above the obstruction, which might be caused by a tumor, developmental anomaly, or some inflammatory process. In communicating hydrocephalus, the ventricular CSF can readily flow into the subarachnoid space; the hydrocephalus results either from an obstruction to its flow within the subarachnoid space or from an alteration in the rate of formation and absorption of the CSF.

CLINICAL ASPECTS OF CEREBROSPINAL FLUID

Cerebrospinal fluid is used for diagnostic testing. Samples of CSF for examination are usually obtained by a *lumbar puncture (spinal tap)* into the *spinal cistern*; this is done by inserting a long needle in the midline between the spines of vertebrae L3 and L4, or L4 and L5, with the patient lying curled up on one side.

There is no risk to injuring the spinal cord because it terminates above these levels. The nerve roots of the cauda equina are usually deflected by the needle and, thus, rarely injured. With the relaxed patient lying sideways, the normal pressure as indicated ranges from 65 to 195 mm of water. The pulsations of the cerebral arteries are registered as small oscillations on the manometer. Compression on the internal jugular veins draining blood from the brain results in a brisk rise in the CSF pressure. A lumbar puncture is contraindicated in the presence of an elevated intracranial pressure or an obstruction in the subarachnoid space. In such cases, removal of CSF from the lumbar cistern would lower pressure below blockage, with several possible results: herniation of (1) uncus of temporal lobe through the tentorium or (2) cerebellar tonsils into the foramen magnum. The former, through pressure on the midbrain, can result in coma and the latter, through pressure on the medulla, can cause death from malfunctioning of the cardiac and respiratory centers.

The removed CSF is examined for the presence of cells (lymphocytes and erythrocytes), plasma protein, gamma globulins, and glucose. Special tests are carried out for specific diseases.

SUGGESTED READINGS

Blaas HG, Eik-Nes SH, Kiserud T, Berg S, Angelsen B, Olstad B. Three-dimensional imaging of the brain cavities in human embryos. *Ultrasound Obstet. Gynecol.* 1995;5:228–232.

Davson H. Formation and drainage of the cerebrospinal fluid. In Shapiro K, Marmarou A, Portnoy H, eds. *Hydrocephalus.* New York, NY: Raven; 1984:p 1–40.

Davson H, Segal MB. *Physiology of the CSF and Blood–Brain Barriers.* Boca Raton, FL: CRC; 1996.

Davson H, Welch K, Segal MB. *Physiology and Pathophysiology of the Cerebrospinal Fluid.* New York, NY: Churchill Livingstone; 1987.

Fishman RA. *Cerebrospinal Fluid in Diseases of the Nervous System.* 2nd ed. Philadelphia, PA: Saunders; 1992.

Laterra J, Goldstein G. Ventricular organization of the cerebrospinal fluid, blood-brain barrier, brain edema, and hydrocephalus. In: Kandel ER, Schwartz JH, Jessel T., eds. *Principles of Neural Science,* 4th ed. New York: McGraw-Hill, 2002; 1288–1301.

McConnell H, Bianchine JR. *Cerebrospinal Fluid in Neurology and Psychiatry.* New York, NY: Chapman & Hall; 1994.

Walz W. *The Neuronal Environment: Brain Homeostasis in Health and Disease.* Totowa, NJ: Humana; 2002.

6
Development and Growth of the Nervous System

Origin of the Nervous System
Establishing Patterns and Regions of the Brain and Spinal Cord
Differentiation of Neurons and Glial Cells
Neural Stem Cells
The Neuron: Early Development Through Maturity
Development of the Cerebellum
Neural Plasticity
Intraneuronal Transport of Signals
Reciprocal Schwann Cell–Axon Interactions
Apoptosis or Naturally Occurring Neuronal Death
Aging of the Brain
Spinal Cord and Peripheral Nervous System
Brain
Critical Periods: Effects of Genetic and Environmental Factors on Development

Individuals are as old as their neurons in the sense that almost all neurons are generated by early postnatal life and are not generally replaced by new ones during a lifetime. The genetically driven development of the complex circuitry of the nervous system continues throughout life, tempered and honed by a combination of constraints readjustments and responses to the influences and demands from both the internal and external environments.

The cardiovascular system and the nervous system are the first organ systems to function during embryonic life. In humans, the heart begins to beat late in the third week after fertilization. Before the heart begins to beat, the nervous system commences to differentiate and change in shape. Growth in size occurs after the heart commences to pulsate and blood slowly circulates to bring oxygen and essential nutrients to the developing nervous system. During the second month, when stimuli are applied to the upper lip of the embryo, there is an avoidance reflex withdrawal of the head. A mother might feel life as early as the 12th prenatal week.

From a relatively few primordial cells present several weeks after fertilization of the ovum, the nervous system undergoes a remarkable change to attain its complex and intricate organization. Once a neuroblast leaves the ventricular layer of the neural tube, not only is it committed to differentiate into a neuron but also it will never divide again. To generate the estimated 100–200 billion neurons in the mature brain requires a calculated production of more than 2500 neurons per minute during the entire prenatal period. The brain of a 1-year-old child has as many neurons as it will ever have. Throughout life, cells are continuously lost at an estimated rate of 200,000 per day in humans. The estimate is based on the observation of the 5 to 10% loss of brain tissue with age. Assuming that there is a 7% loss of neurons over a life-span of 100 years and with

100 billion neurons at 1 year of age, 200,000 neurons will be lost per day. Because the brain has so many neurons, most individuals get through life without losing so many that they become mentally disabled.

The central goal of developmental neurobiology is to gain an understanding of the interactions and resolution of the forces of "nature" versus "nurture". *Nature* is the cell's intrinsic potential contained in the genetic pool to mastermind the neuroblast to attain the full repertoire of cellular processes and features of the mature neurons. *Nurture* refers to the extrinsic epigenetic extracellular factors, both tropic and trophic, that shape the development of the neuron and continue to operate even on the mature neuron.

Differentiation and growth continue postnatally, attaining the organized complexity of the entire nervous system. It continues throughout life as the nervous system is remodeled through plasticity. The totality of events occurring during the development of the brain is not the exclusive property of rigid genetic codes. For example, the human brain probably contains more than one trillion synapses, and there simply is not enough genes, to account for this complexity.

The normal development of a neuron and its subsequent integration into neuronal circuits result from activities at both (1) the *genetic level* and (2) the *epigenetic level*. The former (genetic) comprises (a) transcription or the transfer of information from DNA molecules into RNA molecules and (b) translation or the transfer of information from the RNA molecules into polypeptides. The latter (epigenetic) includes many environmental and extracellular factors that can modify, regulate, or channel subsequent development. Epigenesis involves neurotropic and neurotrophic molecules that have critical roles in the structural changes occurring during ontogeny of the nervous system. Tropic (having affinity for and turning toward) factors are molecules to which, for example, growth cones are attracted (*see* contract guidance in Neuronal Navigation and Development). Trophic (relating to nutrition for survival) factors are molecules secreted by their targets (target-derived neurotrophic factors) and are essential for the differentiation, growth, and survival of neurons. Neurons in part depend on one another for trophic factors, which affect their signaling efficiency and even their survival.

The neurotrophic concept states that during development, neurons are critically dependent for their survival on these target-derived factors. The presence of limited amounts of these factors ensures that only a select proportion of neurons survives and do not succumb to naturally occurring cell death (*see* Apoptosis or Naturally Occurring Neuronal Death) and, thus, the appropriate innervation density of the target is attained. The scenario during development can be categorized as a competitive, yet regulated "battleground" among many influences:

1. The genetic impetus is to produce, during early development, an oversupply of neurons, axons, and dendrites (including their terminal branches) and synapses.
2. The growth of the axons to their target is usually attained by a specific route; however, alternate routes are possible.
3. The projections of the axons from several sources to a specific target neuron or structure (e.g., muscle) is generally diffuse and intermingled in the vicinity of their definitive target.
4. Competition occurs among the oversupply of axonal terminals for appropriate targets (neuron or synapses) with the elimination of supernumerary neurons, axons, and synaptic terminals.

Experimental evidence indicates that developmental changes continue to occur even in old age. Dendrites and axons of neurons of the cerebral cortex of old rats (equivalent in human terms of roughly 75 years) respond to an enriched environment by forming new axon terminals and synaptic connections. Investigations reveal that the structure and chemistry of the brain can be affected by experiences

throughout life, indicating that there is more flexibility and plasticity in neuronal connectivity in old age than previously thought. Thus, the debate over nature or nurture with regard to the brain and behavior is essentially over. Although many details remain to be resolved, both are involved.

ORIGIN OF THE NERVOUS SYSTEM

When the human embryo is but 1.5 mm long (18 days old), the ectoderm (outer germ layer) differentiates and thickens along the future midline of the back to form the *neural plate* (*see* **Fig. 6.1**). With the transfer of certain chemical substances from the underlying mesoderm, the induction of this ectoderm occurs so it is now irreversibly committed to form neural tissue. The neural plate is exposed to the surface and to the amniotic fluid; it is continuous laterally with the future skin. Certain portions of the ectoderm differentiate and thicken in the head region to form *placodes*, which are progenitors of the organs of special sense such as the eyes (optic placode), ears (otic placode), and nose (nasal placode). In fact, the neural plate is a giant placode. The neural plate elongates, and its lateral edges are raised to form the *neural folds* or *keyhole stage* (*see* **Fig. 6.1**). The anterior end of the neural plate enlarges and will develop into the brain. The lateral edges, or lips, continue to rise and grow medially until they meet and unite in the midline, to form the neural tube. This midline union commences in the cervical region and progresses both cephalically and caudally until, in 25 days, the entire plate is converted into the *neural tube* (*see* **Fig. 6.1**). The tube becomes detached from the skin and sinks beneath the surface (*see* **Fig. 6.2**). The cavity of the neural tube persists in the adult as the ventricular system of the brain and the central canal of the spinal cord.

The cephalic end of the neural tube differentiates and enlarges into three dilations called

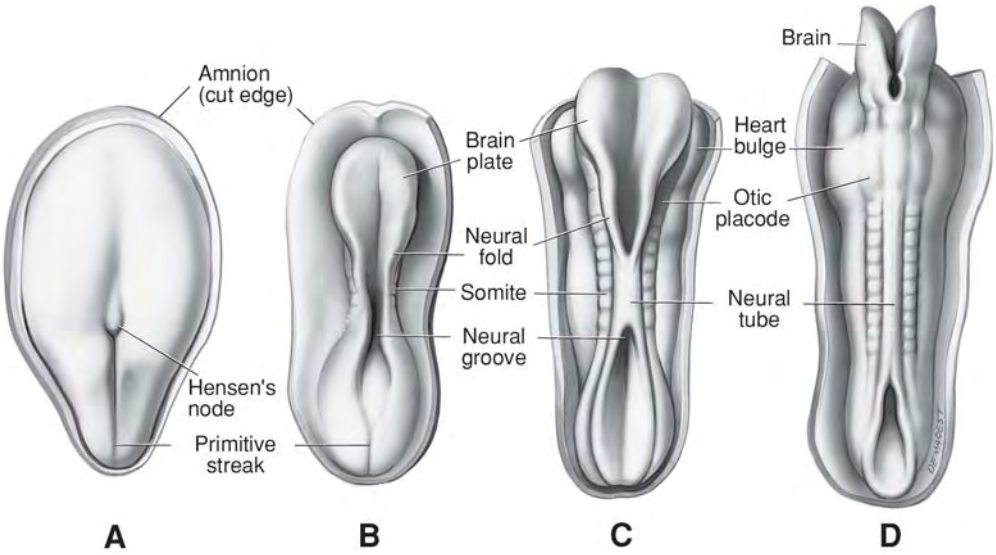


Figure 6.1: Dorsal aspect of human embryo: **(A)** Primitive-streak plate stage of a 16-day presomite embryo; **(B)** two-somite keyhole stage of an approximately 20-day embryo (note the first somites, neural fold, and neural groove); **(C)** seven-somite stage of an approximately 22-day embryo; **(D)** 10-somite neural tube stage of an approximately 23-day embryo.

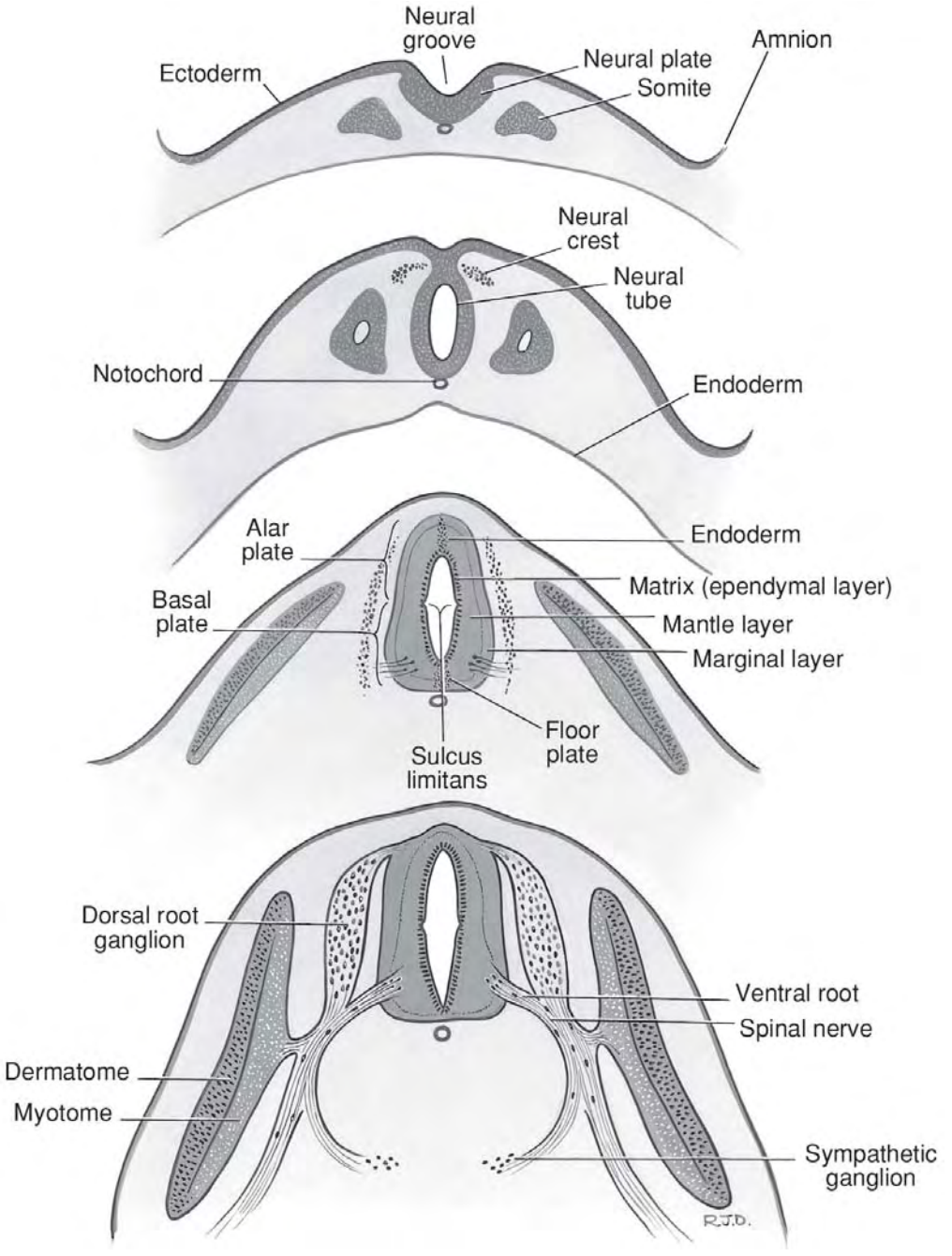


Figure 6.2: Development of the spinal cord, neural crest, somite, and spinal nerve (transverse sections) in a human embryo of the following ages: **(A)** approximately 19 days; **(B)**approximately 20 days; **(C)** approximately 26 days; **(D)** after 1 month. The alar plate gives rise to sensory (afferent) neurons and the basal plate gives rise to motor (efferent) neurons. The sulcus limitans is the boundary between alar and basal plates.

the "primary brain vesicles." Rostrally to caudally, the three divisions are the *prosencephalon* or *forebrain*, the *mesencephalon* or *midbrain*, and the *rhombencephalon* or *hindbrain*. A bilateral column of cells differentiates from the neural ectoderm at the original junction of the skin ectoderm and the rolled edges of the neural plate. These two columns of cells become the *neural crests* (*see* **Fig. 6.2**).

The neural tube is the primordial structure for the central nervous system (CNS) (brain and spinal cord), including all neurons in the CNS, oligodendroglia, and astroglia. The neural crest gives rise to a number of neural and non-neural derivatives. The neural derivatives include (1) neurons in all the sensory, autonomic, and enteric ganglia, (2) cells of the pia mater and arachnoid and the sclera and choroid coats of the eye, (3) neurolemma (Schwann) cells and satellite cells of the ganglia, (4) adrenal medullary cells, and (5) receptor cells of the carotid body. Some neurons of sensory ganglia of cranial nerves V, VII, IX, and X are derived from cells of the otic placode.

Several mesodermally derived elements are associated with the nervous system, including the meninges. Those that secondarily invade the CNS include the blood vessels and microglial cells.

ESTABLISHING PATTERNS AND REGIONS OF THE BRAIN AND SPINAL CORD

The ectoderm of the presomite stage is induced by trophic factors derived from the underlying mesoderm and notochord to differentiate into neuroectoderm and the neural plate that will develop into the CNS. Molecular genetic studies indicate that the development of the early CNS progresses within a program in which genomic transcription factors are involved with neural induction. Furthermore, these studies are revealing the role of genes in establishing the patterns and regions within the nervous system (Hatten, 1999) that activate the genesis of the *anterior–posterior axis pattern* (AP axis, rostrocaudal axis) of the CNS. During early development, there is an *induction pathway* linked to a program of transcription factors that establishes the neuroectoderm and its neuroregulation, or leads to the differentiation of the neural tube and the CNS. The transcription factor program is a determinant resulting in the dominant AP axis pattern of forebrain, midbrain-cerebellum, hindbrain and spinal cord. The *dorsal-ventral axis pattern* is established as the expression of other transcription factors. The dorsalization of specific neural cells types occurs following their induction by locally acting peptide growth factors, whereas the ventralization of other cell types following their induction is by signal regulatory sonic hedgehog factors.

Spinal Cord

The spinal cord comprises 31 segments arranged in an AP axis. The development of the neural tube into these spinal segments is determined by the AP axis and the influences of the AP sequences of mesodermal somites (*see* **Fig. 6.1**). Thus, the basic AP-axis segmentation is derived from an immediate source, namely the dermatome. In turn, each somite and its associated spinal cord segment is integrated into a structural and functional unit consisting of a spinal nerve together with its dorsal and ventral roots, the combination of neural crest and dorsal root ganglion, its sensory dermatomal distribution, and its motor neurons and myotome (*see* **Figs. 7.1–7.3 and 8.1**).

Regional Patterning of the Neural Tube and the Brain

The regionalization of the neural tube into the brain is a *gene expression patterning* resulting in an AP-axis segmentation. However, other multiple gene expression patterns can modify the basic pattern (Rubenstein, 1998). Thus some genes may encode protein factors that regulate the transcription of other downstream genes that, in turn, control cellular differentiation.

1. In the hindbrain and spinal cord, HOX genes (a subset of homeobox genes) appear to

control the identity of cells in the hindbrain as well as the overlapping segmental patterns of the spinal cord and spinal ganglia. The spatial order of the gene expression patterns in the neural tissue is reflected in an orderly distribution of the genes on specific chromosomes. This segmentation is noted in the roots of the spinal nerves (*see* **Fig. 7.1**) and in the brainstem (*see* **Fig. 22.1**).

2. Evidence of this basic axial gene is expressed patterns in the neural plate and early- to mid-gestational developing prosencephalon (forebrain) Thus, gene expression patterns of the forebrain reflect the simpler AP-axial sequences of the neural plate. The complexity of forebrain reorganization apparently results from multiple distinct patterning mechanisms. This indicates that there are several forebrain (prosencephalic) gene expression patterns.

DIFFERENTIATION OF NEURONS AND GLIAL CELLS

The embryonic neural tube eventually comprises four concentric zones: ventricular, subventricular, intermediate (mantle), and marginal (*see* **Fig. 6.3**). The adult nervous system is derived from these basic zones, none of which corresponds precisely to any adult components.

The *ventricular zone* consists of dividing cells. The nucleus of each ventricular cell migrates to the luminal end of the cell (adjacent to the central canal), rounds up, and undergoes a mitotic division; after dividing, the nuclei of the daughter cells migrate to the apical portions of their respective cells, where the replication of its deoxyribonucleoproteins occurs. Thus, the ventricular zone is known as the lamina of the *to-and-fro nuclear movement*. The mitotic and nuclear migration cycle lasts from 5 to 24 hours. Ventricular cells are the progenitors of neurons and macroglia (astroglia and oligodendroglia) of the CNS.

The precursor cells of glial cells can be distinguished from those of neurons by the presence of glial fibrillary acidic protein (GFAP) in dividing glial precursor cells of the ventricular zone. The first glial cells to be formed appear at about the same time as the first neurons. As previously stated, most, but not all, neurons in humans are generated during prenatal life. In

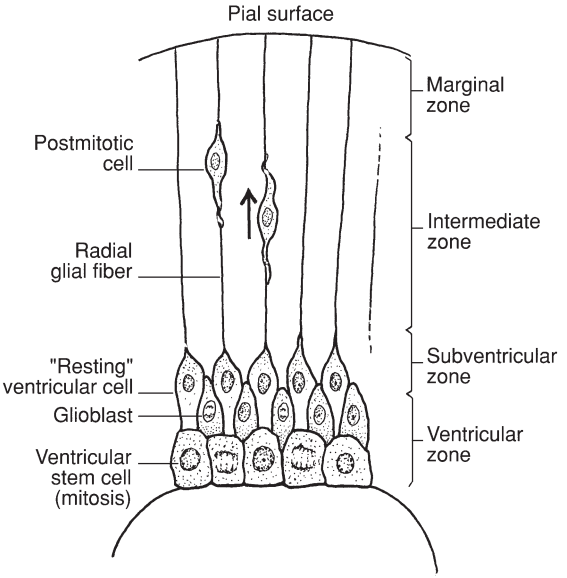


Figure 6.3. The four zones of the embryonic CNS (neural tube). The ventricular cells (stem cells) are derived from neuroectodermal cells of the neural plate. The ventricular stem cells divide into new stem cells that remain within the ventricular zone and others that migrate into the subventricular zone. Within the subventricular zone, the stem cells differentiate either into glioblasts, neuroblasts, or ependymal cells. Some glioblasts differentiate into radial glia cells that extend from the ventricular zone and as a glial fiber to the pial surface of the neural tube. The arrows within the stem (ventricular) cells indicate the direction in which the nucleus migrates to and fro during a mitotic cycle. Arrows outside the cells indicate the direction of the migration of neuroblasts and glioblasts (progenitors of astrocytes and oligodendroglia). The neuroblasts are guided in their migration by the radial glial fibers.

contrast, the precursors of the glial cells retain some capacity for proliferation throughout life.

The *subventricular zone* in time differentiates from the ventricular zone. It is composed of small cells that proliferate by mitosis but do not exhibit the to-and-fro nuclear movements during the mitotic cycles. This zone persists only a few days in the spinal cord, but many months and even years in the cerebrum. It generates certain classes of neurons and macroglia of the CNS. It gives rise to (1) the rhombic lips located on the lateral margins of the medulla and (2) the ganglionic eminence located in the floor of each lateral ventricle. The rhombic lips generate certain brainstem and cerebellar neurons, including the billions of interneurons of the cerebellar cortex (Chap. 18). The ganglionic eminence generates many of the small neurons of the basal ganglia (Chap. 23) and of some other deep structures of the cerebrum.

After these newly differentiated neurons have apparently lost their capacity to synthesize DNA, the mitotic cycle ceases and the cells are triggered to migrate from both the ventricular and subventricular zones into the intermediate zone or even farther to form the cortical plates (*see* below). Never again will these postmitotic cells divide. Those cells that migrate into the rhombic lips and ganglionic eminences, as noted earlier, retain their capacity to undergo mitosis. As a rule, the large neurons differentiate before the small neurons. The large neurons are primarily those whose axons extend long distances, and small neurons (local circuit neurons) are those whose fibers are confined to the region immediately surrounding the cell body.

The *intermediate (mantle) zone* evolves into the gray matter of the CNS, with its complex neural organization. The neurons that migrate and collect to form the cortical plates differentiate into neurons of the cerebral cortex and cerebellar cortex. Most cerebellar cortical neurons are derived from the rhombic lips.

The *marginal zone* is the cell-sparse layer with no primary cells of its own. Eventually, it is invaded by axons, both myelinated and unmyelinated, and macroglia to form much of the white matter.

NEURAL STEM CELLS

Stem cells are "persistent embryonic" cells present even in adults. They have the several potentials of being able to (1) replicate themselves as self-renewal precursors, (2) proliferate large numbers of progeny by neurogenesis, and (3) retain multilineage potential over an extended time. The inner cell mass of the blastocyst consists of embryonic stem cells, which are *totipotential stem cells* with the capability, under proper conditions, to develop into almost any cell type. The germinative zones of the neural tube and the neural crest are comprised of neural stem cells, called *multipotential stem cells* (derivative, progenitor or persistent stem cells (*see* **Fig. 6.3**).

Multipotential *neural stem cells* (NSC) are progenitor cells of the nervous system with the capability of developing into neurons and neuroglia (oligodendrocytes and astrocytes) of the CNS and into neurons, Schwann, cells and satellite cells of the peripheral nervous system (PNS). Note that microglial are mesodermal derivatives. Some NSCs persist and exhibit activity throughout life. . A stem cell is characterized by the combination of both its morphological fate and its functional role. Although NSCs have a high capability for self-renewal in the developing and immature nervous system, they remain quiescent and divide much less frequently in the mature nervous system, but they can resume activity on demand. Thus, NSCs exhibit an impressive power of renewal.

In consort with general biological phenomena, the numbers and activity of the NSCs and their progeny are homeostatically regulated. In adults, persistent neurogenesis of new progenitor neurons from NSCs occurs in the olfactory neuroepithelium (olfactory mucosa), olfactory bulb, dentate gyrus of the hippocampus, and in the prefrontal, posterior parietal, and inferior temporal gyri of the cerebral cortex (Chapter 25). Other locations where NSCs in the adult give rise to derivative cells remain to be uncovered; their capabilities have been questioned and, at best, are markedly reduced. Typically,

many potential NSCs remain quiescent and unrecognized unless activated to supply a need. The fate of the genetic potential of the multipotential NSCs to become neurons or glial cells is expressed in a sequential progression of restriction stages: (1) differentiation into neuroblasts or glioblasts, followed by (2) differentiation into committed neuronal or glial progenitor cells, and, ultimately in adults, into specific neurons or glia.

The precise roles of a variety of molecular factors that regulate and influence the development and ultimate fate of each NSC are incompletely understood. The following are some of the types of molecular factors involved in the potential *resident NSCs* expression of their genetic potential in the sequence of differentiation and restriction stages leading to their fates as committed functional stem cells: (1) *transformation (growth) factors* that modulate during the restriction stages as each cell passes through its development; (2) *signal factors* that act as guideposts during each cell's migration to its destination; and (3) *induction factors* that are involved in the modifications associated with interactions and adjustments to the specific environment of the NSCs.

Stem Cell Therapies

The developmental potentials of NSCs can have significance in regenerative and reparative (cell replacement) therapies. Transplantation of NSCs as donor cells from embryonic and fetal sources into the brain and spinal cord is being evaluated for roles in regenerative therapy and reparative therapy for several neurologic disorders such as Parkinson's disease, Huntington's disease and Alzheimer's disease, as well as for traumatic injuries resulting in, for example, paraplegia. The symptoms of *parkinsonism* are associated with the degeneration of dopaminergic neurons in the basal ganglia (Chap. 24). Neurons obtained from selected sites of aborted fetuses were grafted into the basal ganglia of patients with Parkinson's disease (Bjorklund, in Barinaga, 2000). In many cases, the transplanted fetal tissues (containing either stem or fetal cells) significantly relieved some of the symptoms, including slowness of movement and rigidity. This indicates that survival of transplanted fetal cells into the brain does occur and they have the capacity to express relevant functional activity.

THE NEURON: EARLY DEVELOPMENT THROUGH MATURITY

Neuronal Navigation and Docking During Early Development

The stages involved in the creation of the neuronal network of the brain and spinal cord and its integration with the peripheral nerves during prenatal development are precise and apparently predetermined to a considerable degree. The first two stages are *pathway selection* and *target selection*. In humans, they are instrumental in establishing the basic groundwork of the neuronal networks and pathway systems during prenatal life. The third, the *activity-dependent and experience-dependent stage,* continues throughout life.

Evidence is available that identifies some of the factors involved in assembling, integrating, and maintaining the 100 billion neurons of the human nervous system. Because there are more neurons than genes, each neuron cannot possibly have its own gene to regulate the navigational system controlling (1) *pathway selection* or cell migration from the ventricular layer of the neural tube and (2) *target selection* or the guidance of the growth of axons at their tips (growth cones) as their endings "hone in" to make synaptic connections with their target neurons. The development of the nervous system from the neural plate and neural crest stage to the mature nervous system is synchronized by genetic influences and epigenetic factors. In essence, each neuroblast differentiates into a neuron with its axon terminals, which must *migrate to and dock in its designated site, and be there at the right time to be integrated into a prescribed circuitry.*

At the time a neuroblast commences to migrate from the ventricular zone of the neural

plate, it becomes a postmitotic cell that is (1) incapable of dividing and (2) is branded to become a neuron. The kinetics of cell migration commences as each neuroblast (and glioblast) leaves the ventricular zone at a definite time to navigate to its port of call in the brain and spinal cord. The differentiation of each immature neuron, and the specific path it takes to reach its destination, is determined (1) by the activation of specific sets of genes combined (2) with a variety of epigenetic external signals from other cells in the environment. Initially, the neuroblasts of the brain contact the fibers of the radial glial cells. These are specialized cells, each with a process extending to the ventricular surface and another to the pial surface. The neuroblasts migrate along the scaffolds of these glial fibers by *contact (mechanical) guidance* (*see* **Fig. 6.3**). However, many neuroblasts migrate without the guidance of the glial fibers. Both of these migratory patterns are apparently accomplished with the aid of *tropic molecular cues* or *markers*, which attract the migrating neuroblast or its growing tip. This establishes the basic structural matrix of the brain and spinal cord. In addition, there are *neurotrophic* factors, which are chemical substances released by the targets of neurons. Such factors trigger chemical changes in the neurons that are critical for the survival, differentiation, and growth of neurons. Nerve growth factor (NGF) is the prototypical target-derived neurotrophic factor (family of proteins called neurotrophins) (Chap. 2). Other putative neurotrophins have been proposed. The view that there is a single target-derived neurotrophic factor for each neuron is being modified; more than one factor can presumably influence the development and survival of some neurons. In addition, some neurotrophic factors can be derived from sources other than the target. Once the immature neuron arrives at its destination, the outgrowth of its axon begins. The terminal tip of the elongating axon is the *growth cone* characterized by the presence of finger like projections (filopodia) or flattened extensions called lamellipodia (*see* **Fig. 6.4**). The growth cones act as mobile sentinels. Powered by actin microfilaments, the cones actively explore and probe the tissue environment. Filopodia protrude randomly from the leading edge of the growth cone. Those that extend in the "intended" new direction of growth become stabilized, whereas the others are retracted. Stabilization involves the concentration of actin in the filopodia and a local consolidation of the microtubules in the growth cone. This establishes the new direction in which the axis cylinder continues to elongate. Receptor molecules on the cone's plasma membrane, acting as sensors, are responsive to the diffusible molecules in the vicinity. Chemotrophic factors furnish guidance cues leading to the precision of pathfinding as the axon elongates and sprouts collateral branches. Some guidance cues can be inhibitory and, thus, modulate random collateral sprouting of branches and prevent aberrant growth. The glycoproteins *laminin* and *fibronectin* are growth factors present in the extracellular matrix of both the developing PNS and CNS. The cone responds to molecular cues (chemoaffinity) and *guidepost cells*, which trigger radical turns (even right angle) in the trajectory of an axon and also define the location of branching sites for the development of collateral branches (*see* **Fig. 6.4**). It has been established that growth cones follow cues and markers that are encoded by the cells with which they are in direct contact or that diffuse from target cells. However, the molecular nature of these cues remains elusive.

One of the primary goals of developmental neurobiology is to identify the chemical signals involved with the accurate guidance of growing axons as they establish the basic circuitry of the nervous system. Directing axons to their mark during development is presently conceived to involve, in part, diffusible chemotropic (neurotropic) factors secreted by cells along the designated pathways and target cells. These factors apparently affect the biochemical and functional properties of the receptor sites on the axonal growth cones. This is an expression of *epigenesis*, in which chemotropic factors contribute to the patterns associated with axon

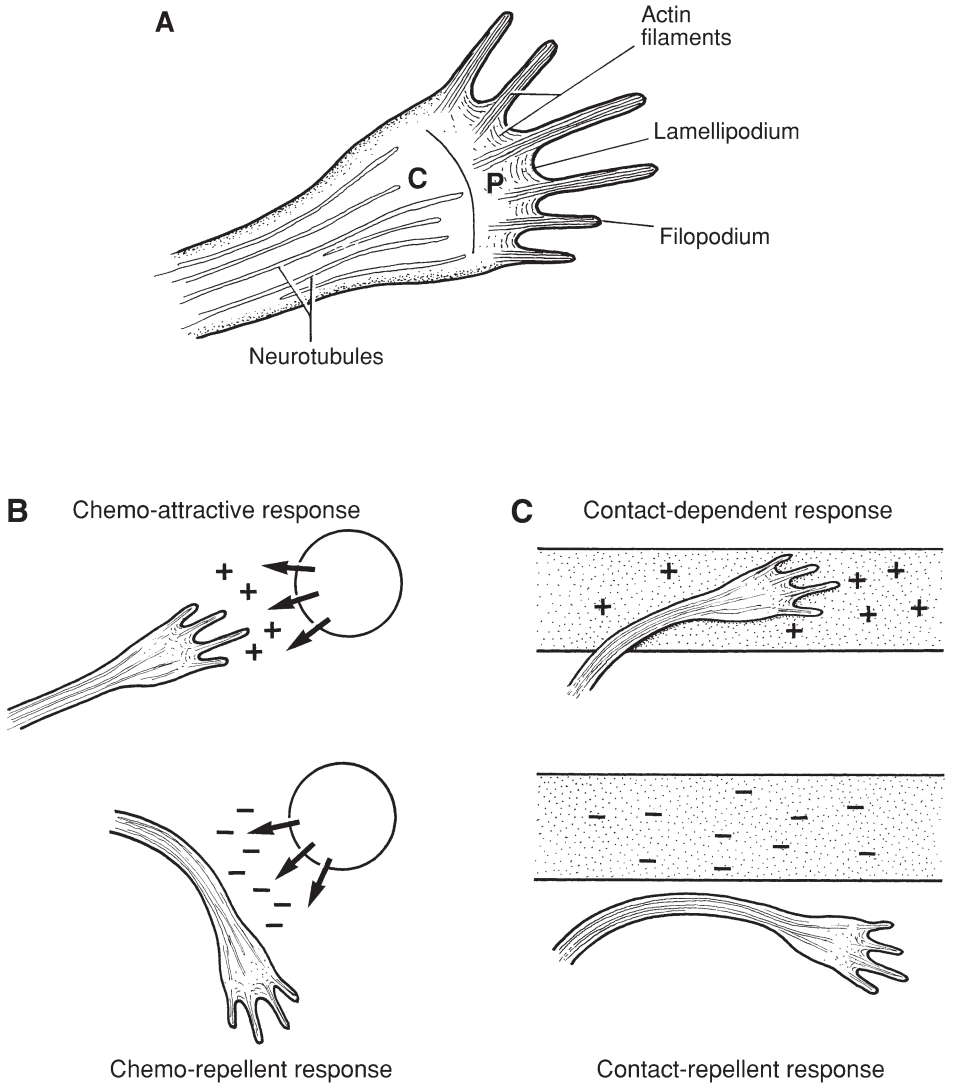


Figure 6.4: (A) Growth cone. The growth cone is a specialized sensory motor structure at the growing terminal of an axon (neurite). (A) Each growth cone is a structure comprised of a *central core domain* (C) and a *peripheral domain* (P) from which extends the leading edge of fingerlike protuberances called filopodia at the base of which are weblike veils called *lamellipodia*; these are shaped by actin filaments (one of the protein filaments of the cytoskeleton). Neurotubules are abundant in the organelle-rich central domain and the actin filaments predominate as tight bundles in the filapodia and as dense interwoven networks in the lamellipodia. **(B)** Directional responses of cones mediated by diffusing guidance molecules from a distant producer site, expressed as attractive or repellent, are called (1) *chemo-attractive (Ch-A)* or (2) *chemo-repellent (Ch-R) responses,* Directional growth responses of the growth cones mediated by direct contact with membrane-bound guidance molecules, expressed as either attractive or repellent, are called (3) *contact-dependent (Co-D)* or (4) *contact-repellent responses (Co-R).*

pathfinding and axon fasciculation (Jessel and Sanes, 2000).

Early differentiation of the nervous system is regulated by a series of chemical inductive signals, some derived from mesoderm. The mesodermal notochord conveys local signals that induce the formation of the floor-plate of the neural tube (*see* **Fig. 6.2**). In turn, the cells of the floor-plate secrete diffusible proteins (axon-guidance factors) called netrin-1 and netrin-2, named for the Sanskrit word for "one who guides" (Kennedy et al., 1994). The axons originating dorsally in the neural tube near the roof-plate grow ventrally to the region near the floor-plate (*see* **Fig. 6.5**). Netrins possess commissural outgrowth-promoting activity signals that cause the growing axons to decussate (cross over) as commissural axons to the contralateral side. The floor-plate apparently releases these factors even when the human embryo is as young as 1 mo old. Thus, they have a role in the act of designating the sites of the decussation of various fiber systems in the spinal cord and brainstem. Examples include the spinothalamic fibers in the anterior white commissure (*see* **Fig. 9.2**) and the internal

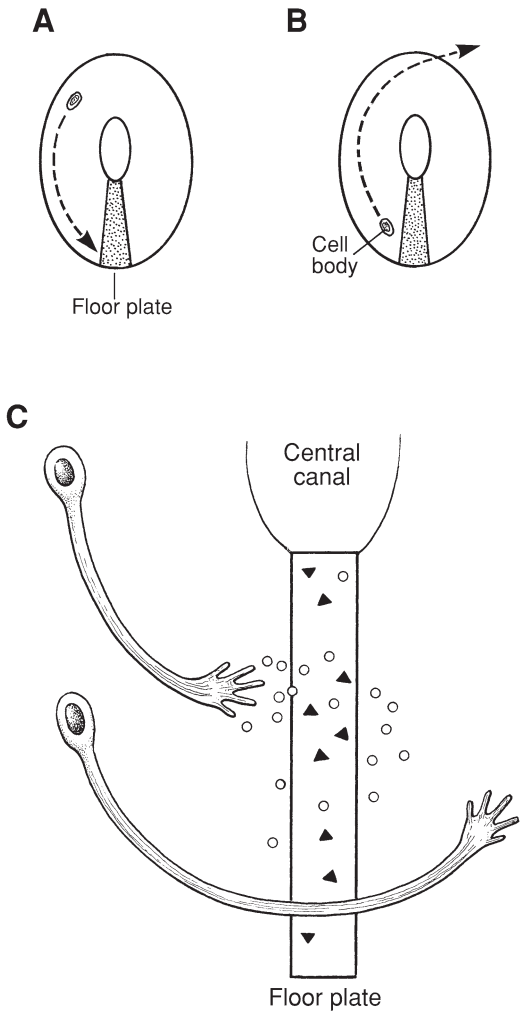


Figure 6.5: (A) In the neural tube, the cell bodies of commissural interneurons are located dorsally. The growth cones of their axons migrate toward the ventral midline in response to cues from attractant guidance molecules of the midline floor-plate. **(B)** In the hindbrain, the cell bodies of the commissural axons of the trochlear (IV) cranial nerve are located ventral to the central canal near the floor-plate before crossing the midline (decussating) dorsal to the floor-plate (*see* **Fig. 13.14**). The growth cones of their axons nerve migrate dorsally toward the midline as a presumed response to the repellent cues of guidance molecules of the floor-plate. **(C)** The decussation of the growth cones of axons of interneurons or of ascending tract fibers (e.g., spinothalamic) results from the attractant axon-guidance factor *netrin* (circles) released by cells in the floor-plate. During the crossing of the floor-plate, the netrin receptors of the axon's growth cones are suddenly silenced by a guidance molecule called "*slit*"(triangles) that activates the "slit" receptor of the growth cone. By the "hierarchical organization of guidance molecules," the activated "slit" receptor silences the netrin receptor to the attractant response netrin, but not the growth-stimulatory response to the netrin receptor (see text). This growth cone is able to continue its growth, decussation, and pathfinding migration as a postdecussated ascending fiber in the growth-permissive microenvironment with its molecular guidance factors within the developing CNS.

arcuate fibers from the dorsal column nuclei that decussate in the medulla to form the medial lemniscus (*see* **Fig. 10.3**).

The glycoproteins, called neural cell adhesion molecules (NCAMs), contribute to the general adhesive properties of neurons that are important as identity sites enabling one neuron to recognize another. An NCAM molecule on one neuron can bind to a counterpart NCAM molecule on another neuron during development of specific populations of neurons. However, NCAM molecules might not have a role in promoting axonal growth. Rather, NCAMs are requisite for anchoring the growth cone to a surface, but not for the directed migration and guidance. The axons and dendrites grow out in a predetermined manner during normal development, with axonal outgrowth preceding dendritic outgrowth. Axons utilizing growth cones as sensors can be conceived as navigating through an epigenetic landscape that guides their growth through reactions to a variety of chemical factors and physical substrates.

In summary, there are presumed to be a variety of (1) outgrowth-promoting protein molecules that stimulate the increase in numbers and lengths of axons—these include such chemotropic factors as laminin and nitrins—and (2) outgrowth-suppressing molecules that have the opposite effect. These chemotropic factors combine to influence the directed migration and guidance of the growing axons to their targets. The NCAMs have an anchoring role to bind the axon to a surface.

The goal of each axon is to make functional synaptic connections with such targets as other neurons (dendrites, cell bodies, and axons) and effectors (muscles and glands). Complex interactions between the nerve terminal and the postsynaptic cell are critical for the initially immature synapse to become stabilized and functionally effective. The growth cone matures into the presynaptic nerve terminal by honing its capability to store and release transmitter spontaneously into a mature terminal with a coordinated response to action potentials. The postsynaptic cell requires some of this differentiation. In turn, the postsynaptic cell is modified by influences from the presynaptic membrane, which regulates the number and distribution of transmitter receptors and other molecules of the postsynaptic membrane.

The interaction of the axon terminal (growth cone) with the plasma membrane of a myotube (immature striated muscle fiber) at a neuromuscular junction (motor end plate) illustrates the influence of the presynaptic terminal on the postsynaptic membrane. Prior to the arrival of the motor nerve terminal, the acetylcholine (ACh) receptors are uniformly distributed over the surface of a muscle fiber. Following the arrival of the future synaptic site, the axon terminal induces the accumulation of a new cluster of ACh receptors on the muscle membrane at the point of ACh release. Some receptors are redistributed as they diffuse within the membrane and become immobilized in the cluster. Others are synthesized anew and inserted within the cluster. Thus, the presynaptic ending controls the synthesis and distribution of receptors on the postsynaptic membrane. A diffusible protein, called acetylcholine receptor-inducing activity (ARIA), has a role in this transformation. Following the clustering of the receptor sites at the motor end plate, the receptors outside of the vicinity of the end plate disappear.

In summary, the precision of the molecularly guided navigation during these two stages is coupled by giving rise to the basic neuronal connections specified by recognition molecules. Thus, the basic connectivity of complex circuitry of the nervous system is established in the sensory systems such as the posterior column–medial lemniscal pathways (Chap. 10), the motor systems such as the corticobulbar and corticospinal pathways (Chap, 11), and other integrating circuits such as those associated with the basal ganglia (Chap. 24). These are presumed to have developed independently of activity or experience.

Oligodendrocytes develop relatively late, always after the growth of the axon in the CNS. This timing is essential because these glia cells

exert inhibitory influences on axonal growth and regeneration. This results from the action of membrane-bound inhibitors of mature oligodendrocytes and CNS myelin.

Activity-Dependent and Experience-Dependent Stage

This stage is involved with refining the coarser features of the circuitry by fine-tuning the patterns of connectivity of the pathway systems through activity and experience. The impetus to accomplish this is through activity and by the experience gained by responding and adjusting to both external and internal environmental stimuli. Many of these connections continue to be capable of modification throughout life. The activity-dependent and experience-dependent plasticity of the ocular dominance columns of the visual cortex is expressed in anatomical and physiological changes during the critical period that results in amblyopia (Chap. 19). Activity- and experience-induced changes in the nervous system are phenomena responding to and associated with the continuous honing of the skills in proficient athletes and musicians. Structural plasticity, axonal sprouting, and the changes in number of dendritic spines can be enhanced (or suppressed) in appropriate neurons through an increase (or decrease) in activity. Engaged exposure to sensory stimulation (e.g., touch or visual) during development can lead to significant increases in the number of dendritic spines and synapses in neocortical neurons of the primary sensory areas (Chap. 25). Even the cortical map of the primary sensory cortex can be modified by activity and experience (Chap. 25). The ability of axons to regenerate in the adult is an expression of the neuron's retention of an embryonic potential throughout life (Chap. 2). A physiological expression of motor learning and skills by the activity of inhibitory synapses is noted in the "importance of inhibition" (Chap. 3). Changes at the molecular level that are associated with memory presumably involve the second-messenger system and modulatory glutamate transmitters acting through NMDA receptors on postsynaptic neurons (Chap. 15).

DEVELOPMENT OF THE CEREBELLUM

The development of the cerebellum presents a dramatic example of the migration of germinal cells (neuroblasts and glioblasts) from two sources navigating along different routes to finally mesh into the intricate circuitry that characterizes the cortex and deep nuclei of the cerebellum (*see* **Figs. 6.6 and 18.3**). Only a few aspects of these precisely timed and integrated sequences will be outlined.

The two sources are (1) the ventricular zone of the neural (cerebellar) plate and (2) the rhombic lip of the dorsolateral lower pons. The routes are (1) direct migration from the ventricular zone to the primordial cerebellum (cerebellar plate) and (2) migration from the rhombic lip to the outer surface (external granular layer) of the cerebellar plate.

The neuroblasts of the ventricular zone migrate into the cerebellar plate to form two strata: Neuroblasts of the deep stratum differentiate into the neurons of the deep cerebellar nuclei (dentate, emboliform, globose and fastigial nuclei), whereas those of the superficial stratum differentiate into the Purkinje cells and Golgi cells (neurons of the cerebellar cortex). Neuroblasts from the rhombic lip migrate over the surface of the cerebellar plate to form the external granular layer. This layer gives rise to the granule cells, basket cells, and stellate cells (neurons of the cerebellar cortex). Glial cells are derived from the same sites as the neurons.

The results of these migrations from dual sources to the right places and arrivals at the right times lead to the formation of the complex integrated circuitry involving the neurons of the cerebellum (*see* **Fig. 6.6**).

The Purkinje cells form their dendritic trees within the molecular layer. At the same time, the granule cells migrate from the external granular layer through the molecular layer to the granular layer (deep to the cell bodies of the

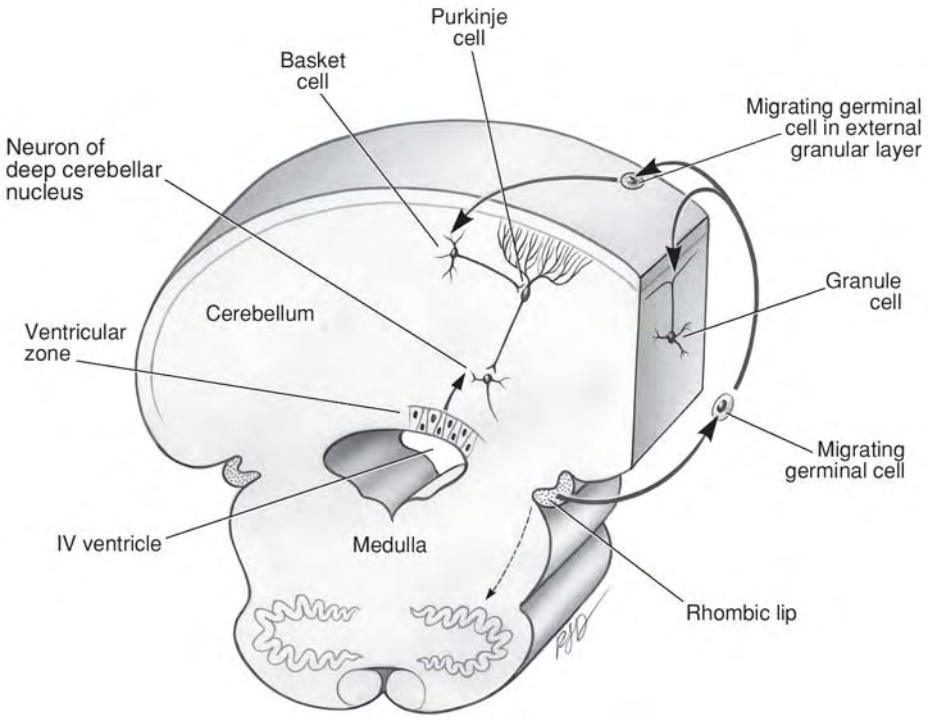


Figure 6.6: The two routes (arrows) of neuroblast migration during histogenesis of the cerebellum.

Purkinje cells). These cells are guided (contact guidance) along the processes of radial glial cells (Bergmann glial cells). Neurotrophic factors and interactions among the differentiating Purkinje cells and granule cells contribute to the events within the molecular layer. Among these are the formation and orientation of the parallel fibers of the granule cells and the complete differentiation of the dendritic trees of the Purkinje cells, as well as the specific connections of these neurons with each other and with other neurons. To these can be added the sequence involving the differentiation, growth, and synaptic connections of the Golgi cells, stellate cells, and basket cells and of the climbing fibers and mossy fibers.

NEURAL PLASTICITY

Neural plasticity is the expression of the capability of the nervous system to modify its morphologic components and their functional roles. As a concept, plasticity involves certain changes occurring in both differentiating and mature neurons, synapses, and networks. Broadly defined, neural plasticity is the potential of both the developing and mature nervous system to change the neural phenotype based on altered patterns of circuits, connections, or activity. Plasticity is operative as a factor in the ability of an organism to alter its behavior in response to novel stimuli from the internal and external environments.

Plasticity is reflected in a neuron's ability to change (1) innately (genetic), (2) in response to stimuli from the environment (epigenetic), and (3) in response to influences from neurotrophic factors. These plasticities are variously specified as *developmental, chemical, neurotrophic, neuronal, synaptic (strength),* and others *(regenerative, adaptive, short or long term, experience-dependent, representational [e.g. body parts],* and *behaviorally induced).*

Developmental Plasticity

Plasticity is active during ontogeny as neuroanatomical and neurophysiological changes as neurons integrate and mature as components of circuits, pathways, and processing complexes (e.g., nuclei and cortices of the sensory and motor systems). Plasticity continues throughout life. For example, neural changes occur within the mature cerebral cortex, whose input and output pathways are dynamically altered in response to a continuous stream of inputs from sensory, behavioral, and experiential activities. Some plasticity is expressed as a means of enhancing and focusing the precision of a neuron's output along with modifications of the neural circuitry, including by pruning surplus collateral branches by microglial phagocytosis.

Chemical Plasticity

The dynamics of the chemistry of the brain has a role in plasticity. For example, the brain is continuously turning over its biochemical constituents that might be involved in coping with changing demands. Radioactive isotope studies reveal the rapidity of biochemical turnover. On the basis of half-life, free amino acids in the brain are incorporated into proteins within 30 minutes. Depending on the particular chemical substance, the rate ranges from a "fast turnover" of a few hours to a "slow turnover" measured in days. In the case of myelin, the half-life of one of its constituents, lecithin, is about 15 days. Proteins, considered to be rather stable, also turn over to a significant degree. A rat replaces about 25% of its brain protein every 30 days, so that by 6 months, only about 1–2% of the original protein remains.

Neurotrophic-Derived Plasticity

During early development, prior to innervating the sweat glands, postganglionic sympathetic neurons are adrenergic (release norepinephrine). Following innervation of the sweat glands by these postganglonic neurons, an interaction occurs with target-derived (i.e., sweat gland) neurotrophic factor that triggers the conversion of these adrenergic neurons to cholinergic ones. This illustrates that neurons are not irrevocably genetically programmed to produce one transmitter. Rather, the choice of transmitter synthesized and released by a neuron can be acquired at a late developmental stage and can be changed to another transmitter by a neuron's environment (MacAllister et al., 1999).

The differentiation of neurons during development can be dependent on and influenced by multiple neurotrophic factors. This applies to neuroblasts, which presumably have an *unrestricted progenitor potential.* Such an embryonic neuroblast (stem cell) is present in the inner layer of the optic cup. Evidence indicates that such a specific neuroblast is prompted by diffusible factors to differentiate into any of the cells of the adult retina, namely rods, cones, bipolar, horizontal, amacrine, retinal ganglion neurons, and also glial (Muller's) cells (Chap. 19). Those developing cells that can differentiate into only one mature neuronal type are called *highly restricted progenitor cells.*

Neuronal Plasticity

Neurons possess the capability of generating new branches (*axonal and dendritic sprouting*), to form new synapses (*synaptic replacement*), to modify synapses (*synaptic change),* and, thereby, to modify neuronal circuits. These features of *neuronal plasticity* are lifelong expressions. The broad concept of learning and memory, including a vast array of coordinated learned movements (e.g., dexterous movements exhibited in music, athletic, and ordinary activities), involve *synaptic plasticity*. These adaptations occur at all levels, including sensory inputs, processing centers (nuclei), pathways, cortical areas, and motor outputs.

Synaptic Plasticity

Electrical synapses do not exhibit plasticity. They are involved with the rapid and essentially stereotyped responses that are the hallmark of electrical *transmission.* Because these synapses are not readily modified and changed in effectiveness, they maintain a stable functional

structure that continuously communicates bidirectionally via ionic currents and gap-junctions channels.

In contrast, *chemical synapses (*those releasing neurotransmitters) exhibit *both short-term* and *long-term plasticity.* They mediate both excitatory and inhibitory activities and, in addition, can produce more subtle and complex behavioral activities than the stereotyped responses of electrical synapses. Because these synapses can undergo short or lasting changes in effectiveness, chemical synapses have an order of plasticity that is significant in such manifestations as from how we move, perceive, and feel to such phenomena as learning memory and other higher functions of the nervous system (learning and memory applies to noncognitive motor skills as well as to cognition).

Synaptic plasticity is expressed as the "strengthening or weakening of synapses," which can be of short or long duration. Short-term or transient changes (e.g., minutes to hours) in the influx or accumulation of calcium ions within the presynaptic terminal can affect the amount of transmitter released. The free-calcium-ion concentration in the presynaptic terminal can be the basis for a number of mechanisms that convey plasticity to chemical synapses. *Short-term memory is associated with transient synaptic plasticity changes and long-term memory with permanent changes*. An emerging view of synaptic plasticity suggests that local neurotrophic action and synaptically associated protein synthesis promotes synaptic remodeling. Evidence indicates that the addition of synapses (increase in synapses per neuron) as well as changes in synaptic structure occur during learning and memory.

Synaptic Plasticity and Dendritic Spines

Several features make dendrites, especially those with spines, basic to an understanding of learning and memory. These features are as follows: (1) About 90% of all synapses are with dendrites; (2) plasticity changes result in strengthening or weakening the synapses; (3) spines are characterized as *multifunctional integrative* units; in vivo imaging has demonstrated that spines can form, collapse, and reform and also change in size and shape rapidly in response to a diverse array of stimuli and thereby exhibit activated-dependent plasticity (Chap. 3).

A generalization is emerging that the more recently phylogenetically evolved parts of the brain, those concerned with higher neural functioning, are more flexible or plastic than the older parts of the brain. This plasticity is reflected in the ability of certain parts of the brain to reorganize itself after damage and to recover function. Stated in cellular terms, neurons in some newer parts of the brain are more capable of extending new branches and forming new synapses than neurons in other parts of the brain (Dowlng, 1993). The capacity for functional plasticity is maintained throughout old age.

The biological expression of each person's individuality is based on a distinctive genetic constitution combined with unique epigenetic modifications involving a degree of plasticity.

INTRANEURONAL TRANSPORT OF SIGNALS

Anterograde and retrograde transport convey macromolecules, including trophic factors, that are involved in such roles as general maintenance of the neuron, axonal growth during development, axonal remodeling as an expression of plasticity, and regeneration of injured neurons (Chap. 2). These transport systems are essential for coordinating the complex functional interrelations between the cell body and the entire axon and dendrites, especially because macromolecules are synthesized in the cell body. Some macromolecules are thought to convey signals (*signal peptides*); that is, they act as messengers with roles in influencing various aspects of the neuronal processes. Newly synthesized macromolecules by each neuron are delivered from the cell body, via the *anterograde transport pathway* in the axon, to sites where these proteins are utilized by the neuron throughout its life history, from early development through maturity.

Indications are that neurons utilize the *retrograde transport pathway* to convey signal peptides generated by events (e.g., axon injury) in the axon to the cell body and nucleus of the neuron. Means of conveying information from the sites of axonal growth, reorganization, and injury are essential because axons have a limited capacity for synthesizing macromolecules. Retrograde communication can influence activity, for example, in the gene transcription essential for supplying macromolecules required for axonal repair, regeneration, and plasticity, and even learning (Ambron et al., 1995). This rapid retrograde transport is a system by which the needs of each axon are continuously communicated to the biosynthetic centers of the neuron. Another role of signals is to inform the cell body of the neuropeptide transmitter stores in the axon terminals and to adjust the activity of the biosynthetic centers of the cell body to maintain adequate supplies of transmitters in the terminals (Chap. 3).

RECIPROCAL SCHWANN CELL–AXON INTERACTIONS

From the early stages of development through old age, *reciprocal Schwann cell–axon interactions* occur with profound effects by one on the other. The vehicles for these activities are signal molecules (information carriers) that are (1) generated by Schwann cells to and act on neurons or (2) generated by neurons and their axons to act on Schwann cells. Among these signal molecules are neurotrophic factors involved with growth and survival. Neurons and Schwann cells are critically dependent on signaling mechanisms of immense and subtle complexity. Although less well documented, significant glial cell–axon interactions are also presumed to occur.

The Schwann cells influence the differentiation and growth of axons. Their released soluble factors have roles in guiding the growing axon, promoting its maintenance, and ensuring its survival. The ensheathment and myelination of both unmyelinated and myelinated axons are specially regulated by contact with axons. This relationship is essential for the conduction of the nerve impulse. The Schwann cells play a critical role in several aspects of axonal regeneration in the PNS. The ability of these cells to promote the regenerative efforts of the CNS (Chap. 2) has stimulated interest in using Schwann cells as autographs for CNS repair.

The neuron through its axons exerts, through chemical factors, influences that can (1) stimulate differentiation of Schwann cells, (2) induce and repress the proliferation of Schwann cells, and (3) modify the migration and growth of Schwann cells. By these means, the appropriate placement in functionally relevant numbers of Schwann cells is reached during development, maintenance and regeneration.

The relation of Schwann cells and axons is not stereotypic, as demonstrated in several variants form the typical nerve with each fiber ensheathed by its own Schwann cells. In unmyelinated fibers, the usual pattern of ensheathment is for the Schwann cell to harbor a number of nerve fibers within individual channels continuous with the Schwann cell surface (*see* **Fig. 2.8A**). A variant occurs in the olfactory nerve, where clusters of groups of fine fibers are enclosed in troughs communally within the Schwann cell (*see* **Fig. 2.8B**). Another is in the enteric plexus of the gut (autonomic nervous system; Chap. 20, **Fig. 20.4**), where enteric glia cells (equivalent of Schwann cells) ensheathe both the cell bodies and their processes.

APOPTOSIS OR NATURALLY OCCURRING NEURONAL DEATH

The life cycle of neurons consists of mitosis, differentiation, migration, maturation, and death. During development, massive numbers of neurons are lost as a result of a process called *apoptosis (programmed cell death, physiological cell death [PCD]).* Apoptosis is conserved throughout evolution, occurring in such forms as nematode worms, with which important insights were derived. The purpose of

apoptosis is the removal of surplus or damaged cells. It is essential for development and tissue homeostasis, and when dysregulated, it can result in cancer, neurodegenerative disease, or autoimmunity.

Control of Survival or Death of Neurons

During ontogeny, at least half of all neurons do not survive; they die via programmed cell death. The morphologic features of apoptosis are cell shrinkage, condensation and clumping of nuclear (DNA) chromatin, cellular fragmentation into discrete granular masses, and phagocytosis of cellular remnants by macrophages. This contrasts with necrotic cell death following traumatic injury in which there is early dilatation of the nucleus with scattering of chromatin against the nuclear membrane, rapid hydrolysis of the cell membrane, and dilatation and fragmenting of cytoplasmic organelles.

The nervous system sculpts excess neurons in order to maintain a precisely regulated homeostasis for the steady-state preservation of neuronal organization and optimal functioning of the nervous system during development. This neuronal suicide is accomplished by activating intrinsic biochemical and molecular mechanisms. Astrocytes, oligodendroglia, and Schwann cells also undergo programmed cell death. Apoptosis is essential in eliminating superfluous neurons and injured neurons associated with disease-related deterioration or neuronal damage resulting from toxic exposure, low oxygen, or traumatic injury. The debris is removed by the macrophages that act as scavengers of the immune system's cleanup crew. This suggests that neurons are initially overproduced and then are required to compete for the just normal amount of available target-derived neurotrophins. Consequently, some neurons succumb by apoptosis.

The differentiation and survival of neurons and glia require *trophic support*, which appears to be dependent and promoted by the critical action of multiple protein neurotrophic factors produced by target cells. Nerve growth factor (NGF), the first described, is one of many that have been divided into several classes: (1) neurotrophin class (NGF, *neurotrophin 3, neurotrophin 4/5,* brain-*derived neurotrophic factor)*; (2*)* interleukin 6 class (e.g., *ciliary neurotrophic factor)*; *(*3) transforming growth factor α class *(e.g., glial-derived neurotrophic growth factor)*; (4) fibroblast growth factor class; and (5) hepatocyte growth factor class. Genes encode neurotrophic factors and their receptors on target cells.

Apoptosis is orchestrated and tightly regulated by interconnected biochemical pathways involving protein factors that act either as "death" activators or as "death" inhibitors. The potential role of apoptosis during development includes the reorganization of neuronal branches, including synaptic connections, in addition to removal of unnecessary neurons. Early cell death is a possible destiny for any neuron, but this fate can be circumvented by avoiding apoptotic signals or by receiving appropriate survival signals from *neurotrophins.* Apoptosis has been characterized as a *default pathway* for all cells, and only by receiving the appropriate survival signals can neurons or glia escape. *Genes* encode several components of the biochemical machinery of *apoptosis*. This cell death in the mammalian nervous system is activated by intracellular and extracellular apoptotic signals that control biochemical pathways involving families of caspaces. In the living cell, caspaces exist as inactive proteolytic enzymes (zymogens), and when activated, they can cleave substrate proteins by a proteolytic program that mediates apoptosis.

Originally, neurotrophic factors were believed, as noted by their name, to promote the survival of neurons by stimulating their metabolism in beneficial ways. However, gene-targeted studies have demonstrated that the survival of neurons also is dependent on neurotrophins, which act to suppress an *endogenous cell death program*. This is accomplished by a biochemical linkage between a neurotrophic factor that inhibits the signaling cascade activating caspaces. Elimination of neurotrophins and their receptors leads to neuronal death by loss of trophic support.

From Genes to Survival or Apoptotic Death

Genes encode the neurotrophic factors and their receptors to initiate the molecular basis for trophic support by the neurotrophins. The genetically mediated neurotrophins are integral to the assemblies of neurons that are dependent on the cell-to-cell interactions and, more specifically, by the neuron-to-target-cell interactions, for neuron survival during development. As such, the neurotrophins are regulators of development, maintenance, and function of the nervous system. The "survival genes" are dependent on neurotrophins to protect neurons from apoptotic death by inhibiting the activation of the caspace-generated biochemical cascades. The "death genes" promote the programs that activate the families of proteases called caspaces, which are central to the death cell role. Activation of caspace enzymes leads to the proteolytic activity of substrate proteins within the neuron, leading to apoptosis.

During ontogeny, by limiting the quantity of neurotrophins to an appropriate amount, the neurotrophin can function in a survival mode to ensure a match between the viable number of surviving neurons and the requirement for appropriate target innervation to meet the functional demands of the neuron.

Some basic elements relevant to the caspace biochemical pathways associated with activation or inhibition of apoptosis are outlined. The caspaces comprise over a dozen members (caspaces are derived from pro-caspaces). They cleave numerous types of protein, producing many products essential to neuronal viability. A number of stimuli can trigger apoptosis by activating caspaces to act as the "executioners" of neuronal death apoptosis. Neurotrophins suppress endogenous death programs. The binding of neurotrophins to tyrosine kinase receptors is considered to trigger the activation of a biochemical pathway leading to the phosphorylation of protein substrates that inhibit caspace activity to thereby avoid apoptosis. Neurotrophin deprivation triggers caspace activation and a fate by apoptosis. Possibly this deprivation permits cleavage of pro-caspace, resulting in apoptosis. Insufficient neurotrophins allows for the dominance of the "death genes."

In addition, neurotrophins fine-tune and regulate axon growth, dendritic pruning, and patterning of the innervation with other neurons and effectors (i.e., muscle cells) and the expression of proteins in normal neuronal function (neurotransmitters, channels, neurotubules, and others). In the mature nervous system, neurotrophins are thought to have some control over synapse function and neuronal plasticity. Simultaneously, they modulate neuronal survival.

Apoptosis in Neurodegenerative Diseases

Degeneration occurring in Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis might be associated with apoptosis. These diseases have the following in common: (1) There is a familial form with Mendelian inheritance patterns, (2) there is selective degeneration of particular neuronal types, and (3) all are associated with cellular or extracellular degeneration aggregates.

AGING OF THE BRAIN

The number of neurons tends to decrease with age, for as neurons die, they are not replaced by new neurons. The consequences of a slight loss are not necessarily noticeable because the remaining neurons can functionally compensate for a small decrease in numbers.

The brain is said to decrease gradually in weight over the years, losing as much as 10% between the ages of 20 and 90 years. This is presumably related to the loss and atrophy of neurons and glia and to the decrease of extracellular spaces. The loss of cells varies from region to region, with the brainstem exhibiting only a slight decline and the cerebral cortex undergoing the greatest loss. Some evidence indicates that the decrease in weight and the degree of cortical atrophy in healthy old individuals who have no neuropathological condition in the brain is relatively slight. Within the cerebral cortex, the loss of neurons is greatest

in the neocortex of the frontal pole, precentral gyrus, cingulate gyrus, and primary visual cortex.

Neurons undergo senescence. Aging of neurons is evidenced by a change in size (either decrease or increase), by the accumulation of pigment, or by a decrease in amount of Nissl substance. In humans, the quantity of ribonucleoproteins in the alpha motoneurons of the spinal cord increases significantly from birth to 40 years of age, plateaus from 40 to 60 years, and decreases thereafter. In elderly people, the decrease in the weight of the brain, increase in the size of the ventricles, and calcification in the meninges are all signs of an aging nervous system.

An indication of the degree of the aging process after the prime of life is obtained by comparing several parameters in the 30-year-old age group with those in the 75-year-old group. In the older group, the reduction in brain weight is about 10%; in the blood flow to the brain, about 20%; in the number of nerve fibers in large nerves, about one-third; in the number of taste buds, about two-thirds; and in the velocity of nerve conduction, about 10%. The last correlates with the observation that the rate and magnitude of reflex responses to stimulation decrease with age.

SPINAL CORD AND PERIPHERAL NERVOUS SYSTEM

Up to about the third fetal month, the spinal cord extends throughout the entire length of the developing vertebral column. At this time, the dorsal (sensory) roots and the ventral (motor) roots of the spinal nerves extend laterally at right angles from the spinal cord. The roots unite in the intervertebral foramina to form spinal nerves. The roots and spinal nerves are products of outgrowths from the spinal cord and neural crests (*see* **Fig. 6.2**). Because the growth in length of the bony vertebral column exceeds that of the spinal cord during fetal and early postnatal life, the spinal cord after the third fetal month becomes relatively shorter than the vertebral column. This is accompanied by an elongation of the roots of the spinal nerves between the spinal cord and the intervertebral foramina.

At birth, the caudal end of the spinal cord is located at the level of the L3 vertebra, and at adolescence, as in the adult, the caudal end is at the level approximately between the L1 and L2 vertebrae. As a result of this disparity in growth, the lumbar, sacral, and coccygeal roots become directed caudally at an acute angle to the spinal cord. The subarachnoid space below the first lumbar vertebra in the adult is occupied by dorsal and ventral roots of spinal nerves (cauda equina) and by the filum terminale, not by the spinal cord (*see* **Fig. 7.1**).

Adjacent to the neural tube are 31 pairs of somites. These are embryonic structures that differentiate into muscles, skeleton (including the vertebral column), and connective tissues (*see* **Figs. 6.1 and 6.2**). The somites are segmental (metameric) structures arranged in sequence from the first cervical through the coccygeal levels. By segmental is meant a repeating unit of similar composition.

Each pair of nerves develops in association with each pair of somites. The apparent segmentation of the spinal cord is dependent on the development of the paired segmental spinal nerves. The bilateral neural crest also becomes segmented into paired units, one pair for every future sensory (dorsal root) ganglion of each spinal nerve.

BRAIN

Prenatal Development

Early in the second fetal month, the "three-vesicle brain" differentiates into a "five-vesicle brain" (*see* **Fig. 6.7**). The prosencephalic vesicle is subdivided into the telencephalon, or endbrain, and the diencephalon, or between (twixt) brain. The mesencephalic vesicle remains as the midbrain; the rhombencephalic vesicle is subdivided into the metencephalon, or afterbrain, and the myelencephalon, or spinal brain.

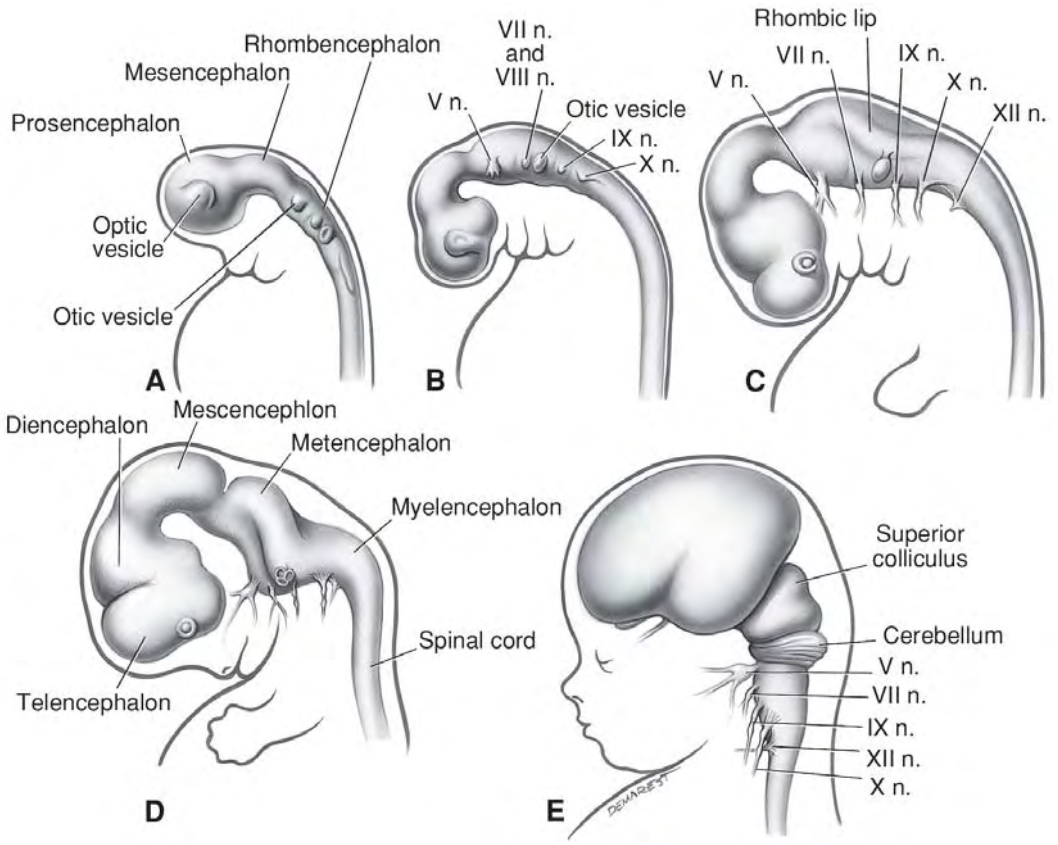


Figure 6.7: Human brain (lateral view): **(A)** 3-week embryo; **(B)** 4-week embryo; **(C)** 5-week embryo; **(D)** 7-week embryo; **(E)** 11-week fetus. (Adapted from Corliss.)

The development of the "contorted" brain from the tubelike structure is the result of the complex integration of several processes: (1) three bends known as flexures, (2) differential enlargement of the different regions, (3) growth of portions of the cerebral hemispheres over the diencephalon, midbrain, and cerebellum, and (4) the formation of sulci and gyri in the cerebral and cerebellar cortices (*see* **Figs. 6.7 to 6.9**). The flexures are the mesencephalic (midbrain) flexure (forming an acute angle on the anterior surface of the brain), the pontine flexure (forming an acute angle on the posterior surface), and the cervical flexure at the lower medulla (forming an acute angle on the anterior surface). The posterolateral margin of the rhombencephalon is the rhombic lip, which develops into the cerebellum. The differential enlargement is most pronounced in the cerebral and cerebellar hemispheres. The telencephalon during development surrounds most of the diencephalon; there is an intussusception (telescoping) of the diencephalon into the telencephalon (*see* **Figs. 6.7 to 6.9**).

At the end of the third fetal month the main outlines of the form of the brain are recognizable and the external surface of the cerebrum is still smooth. Fissuration commences in the fourth fetal month with the appearance of the lateral sulcus of the cerebrum and posterolateral sulcus of the cerebellum separating the nodulus and attached flocculi from the vermis of the posterior lobe (*see* **Fig. 18.1**). The central sulcus, calcarine sulcus, and parietooccipital

sulcus are indicated by the fifth fetal month; all of the main gyri and sulci of the cerebral cortex are present by the seventh fetal month. The external structure of the cerebral hemisphere of the 8-month fetus is characterized by the prominence of the precentral and postcentral gyri, by a wide-open lateral sulcus exposing the insula, and by the presence of all primary and secondary sulci and a few tertiary sulci. The occipital lobe overrides the cerebellum. During the last month of fetal life, the frontal and temporal lobes are stubby, the insula is still exposed to the surface, and the occipital poles are blunt. The cortical gyri are broad and plump,

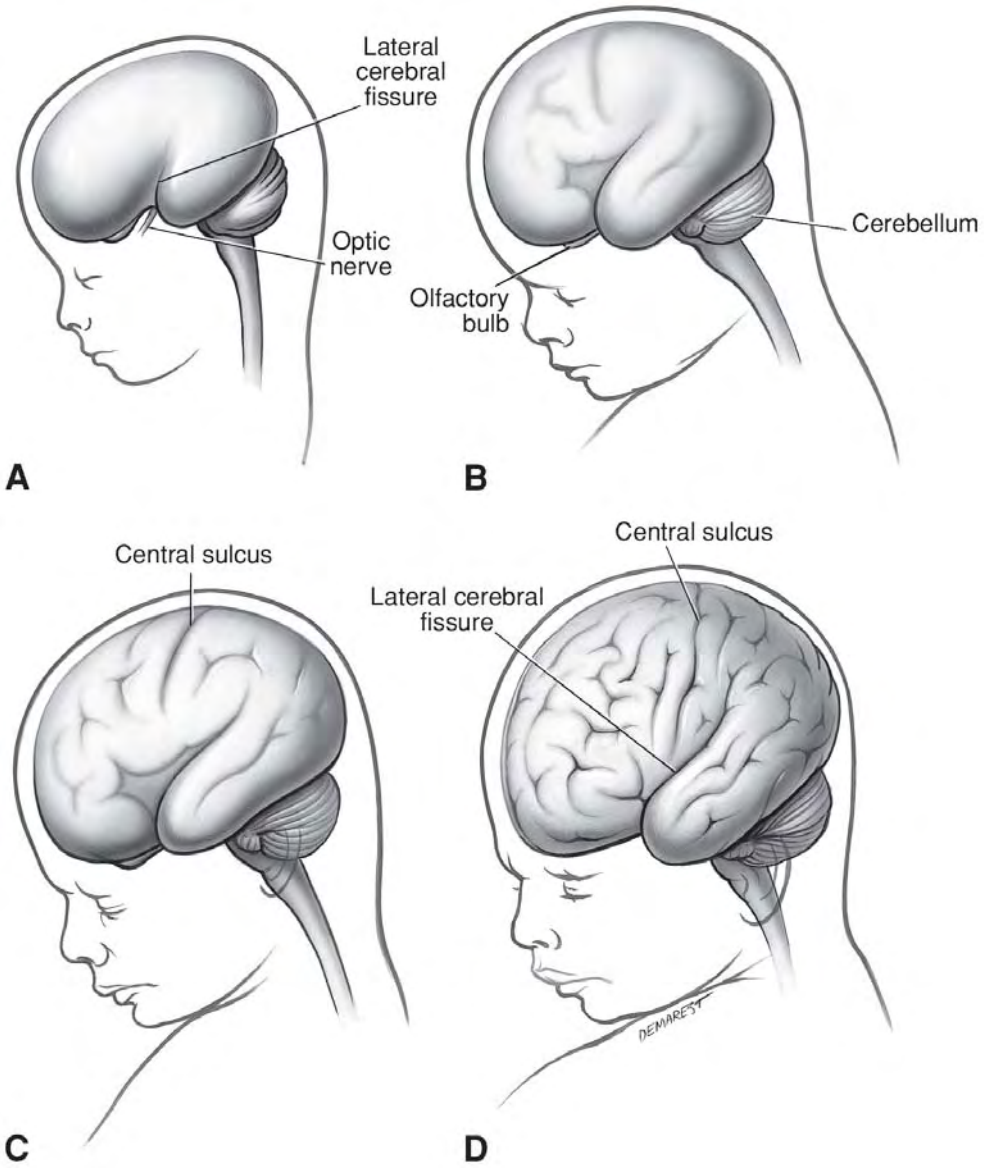


Figure 6.8: Human brain (lateral view): **(A)** 4-month fetus; **(B)** 6.month fetus; **(C)** 8-month fetus; **(D)** newborn infant. (Adapted from Corliss.)

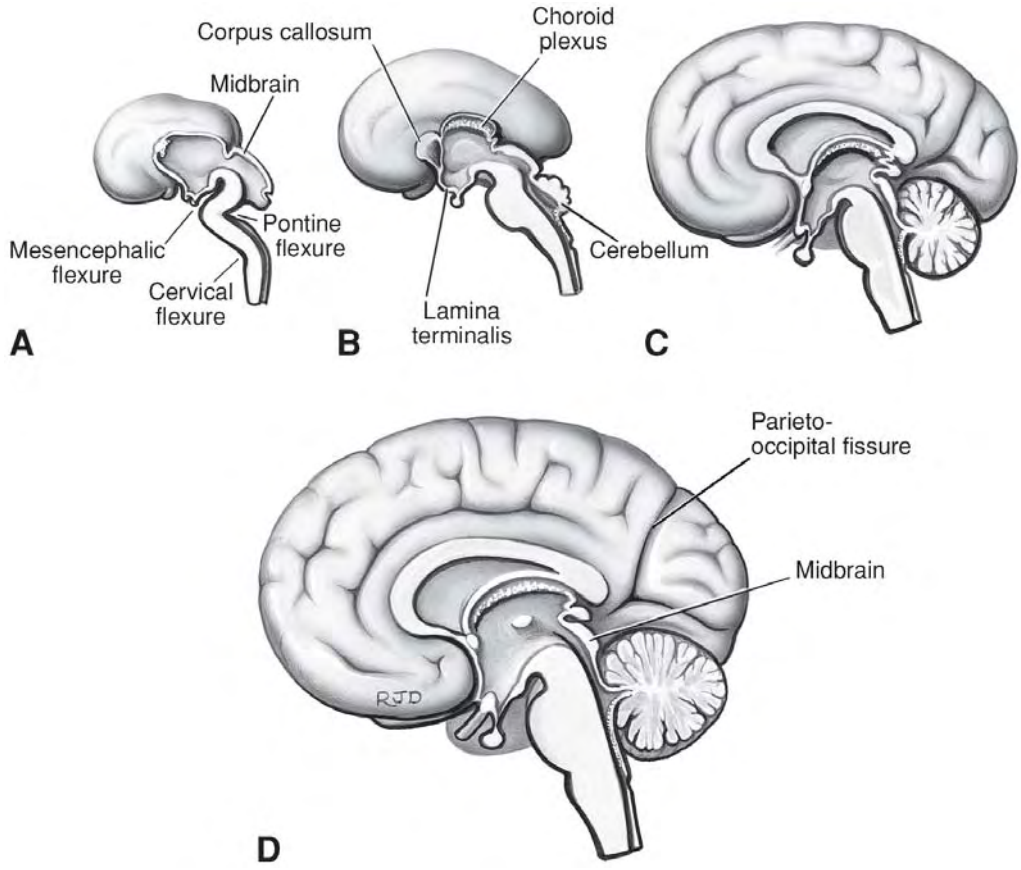


Figure 6.9: Human brain (midsagittal view): **(A)** 3-month fetus; **(B)** 4-month fetus; **(C)** 8-month fetus; **(D)** newborn infant.

and the fissures are shallow. The patterns of the primary and secondary sulci are simple.

The cerebrum of the full-term neonate is more fully developed in the regions posterior to the central sulcus than in the anterior regions. The frontal pole and the temporal pole are relatively short, and the insula is almost completely covered by the adjacent lobes. The number of tertiary sulci is still small. The pia mater is not completely adherent to the brain and does not dip into all the sulci. The superficial blood vessels are straight. The brain has a gelatinous consistency. The cortex is poorly demarcated from the white matter. By the end of infancy, at 2 years of age, the relative size and proportions of the brain and its subdivisions are essentially similar to those of the adult brain. The brain is firmer. The gray cortex is demarcated from the subcortical white matter, which is now myelinated. The superficial cortical blood vessels are predominately tucked into the fissures and sulci. After the end of the second year, the tertiary sulci dominate the topographic pattern of the cerebral surface. These sulci are variable from brain to brain and thereby put the stamp of individuality on each brain. Tertiary sulcation can continue throughout life.

Postnatal Growth

The large brain in the newborn infant exceeds 10% of the entire body weight; in the

adult, the brain constitutes only approximately 2% of the total body weight. The postnatal growth of the brain is rapid, especially during the first 2 years after birth. The brain weighs about 350 g in the full-term infant and about 1000 g at the end of the first year. The rate of growth slows down after this, and by puberty, the brain weighs about 1250 g in girls and 1375 g in boys. It appears that the brain of a girl grows more rapidly than that of a boy up to the third year, but the brains of boys grow more rapidly after that. This brain size is reflected in the growth of the cranial skeleton. In contrast to the adult, the young child has a large cranium in relation to the face. Head circumference is a measure of the growth of the brain. The head circumference is 34 cm at birth, 46 cm at the end of the first year, 48 cm at the end of the second year, 52 cm at 10 years, and only slightly larger at puberty and in the adult.

CRITICAL PERIODS: EFFECTS OF GENETIC AND ENVIRONMENTAL FACTORS ON DEVELOPMENT

Of all the malformations and congenital defects in human beings, ranging from minor observable variations from the norm to lethal abnormalities, as many as one-half are estimated to involve the nervous system. Although the entire nervous system develops as an integrated organ system, its various parts and subparts maturate at different rates and tempos. During ontogeny, each structure passes through one or more critical period, during which it is sensitive to various influences. These periods are generally times of rapid biochemical differentiation. At such a period, the proper influences have a significant role in advancing normal development. When normal influences are wanting or when abnormal influences are exerted at these critical times, subsequent normal development is often impaired. When the impaired development results in anatomic abnormalities that are present at birth, they are called *congenital malformations*. These abnormalities are usually caused by genetic factors (chromosomal abnormalities or mutant genes) and environmental factors.

Genetic Factors

Many cases of congenital mental deficiency and retardation are the result of trisomy of autosomes (three chromosomes instead of the usual pair). *Down syndrome (mongolism)* is a genetic condition in which there are three copies of chromosome 21.

Another genetic disease, *phenylketonuria (PKU)*, is a clinical syndrome of marked mental retardation associated with irritability and abnormal electroencephalogram (EEG) patterns. This condition is the result of an inherited inborn error of phenylalanine metabolism (transmitted by an autosomal recessive gene) that results in an excessive accumulation of the amino acid phenylalanine and its metabolites. The basic defect is a deficiency of the enzyme phenylalanine hydroxylase in the liver; it is essential for the conversion of phenylalanine to tyrosine. Treatment consists of placing PKU patients on a low-phenylalanine diet commencing in the first year of life; it must be done at this time because the brain damage caused by this condition is the result of the accumulation of excess phenylalanine, which reaches its peak between the second and third years of life.

Nutrition

Malnutrition and undernutrition during fetal life, infancy, and childhood have an effect on the developing nervous system. Certain nutritional deficiencies, especially those occurring at the critical early rapid period of maturation, can result in permanent damage. In humans, the critical period extends from the second trimester of pregnancy through most of the first year after birth. During this interval, many neurons and macroglia are being replicated and much of the brain growth is taking place. Evidence indicates that under severe protein malnutrition, the rates of proliferation of new neurons and glial cells are reduced. This reduction occurs during fetal life because even the fetus is not protected from maternal malnutrition. The developing brain is vulnerable during

the remainder of this critical period of postnatal life; the formation of glial cells is impaired, and myelination is inefficient. Severe malnutrition during this period in human infants is known as *marasmus*. If the child is fed a nutritionally adequate diet after this period, the damage is not completely repaired, even though normal appearance can be achieved in some subjects. Those who appear to be healthy have brains, that could be damaged by the protein deficiency. The functional abnormalities in children reared on nutritionally inadequate diets could consist of transient apathy, lethargy, or hyperirritability, together with a lesser intellectual development as measured by a decrease of some 10–20% of mental capacity.

Prolonged protein deficiency in children from 1 to 2 years of age can result in *kwashiorkor*. In this condition, the number of neurons is not reduced, because the deficiency occurs after the full complement of neurons is formed; however, the complete differentiation and connectivity of cortical cells could be impaired. If, after being subjected to prolonged, severe malnutrition, children with kwashiorkor are fed a normal diet, their IQ test scores still remain below those of other children in the same population, including siblings who were not subjected to severe malnutrition.

The timing of nutritional deprivation is a critical factor in determining whether or not subsequent recovery from the effects of such deficiencies is possible. In contrast to brains of fetuses and young children, the brains of adolescents and adults are more resistant to permanent effects of malnutrition. The young and mature adult victims of starvation during World War II did not show any loss of intelligence after their nutritional rehabilitation.

The effects of malnutrition assume gigantic proportions in the world today. Roughly 60% of the world's preschool population (over 500 million children) are exposed to varying degrees of undernutrition. These children live primarily in underdeveloped lands on diets low in proteins and calories. Malnutrition is contributory to the early death of many of them. Survivors grow up in poverty and become adults with physical and mental handicaps. Thus, these poverty (nongenetic) conditions are perpetuated through their children—to be passed down from one generation to the next.

Hormones

The mental retardation associated with cretinism in humans is the result of a thyroid hormone deficiency at a critical period during the late stages of *in utero* development (estimated to begin at the seventh fetal month). The cerebral cortex of cretinoid individuals is poorly developed. There is a reduction in the number and size of neuronal cell bodies, as well as hypoplasia of both their axons and dendrites. Mental retardation of the cretinoid human child can be prevented or effectively remedied if adequate doses of thyroid hormones are given during the first year of life.

Amblyopia (Lazy Eye)

Amblyopia, or lazy eye, is a condition of reduced visual acuity caused by inadequate stimulation of the macula of one eye by formed objects between the second and fourth years of age. It results in a defect in the image viewed by the macula of the affected eye. The slightly cross-eyed child favors one eye over the other to avoid seeing double (diplopia). In response to the altered balance of visual output from the two eyes, long-lasting anatomical and physiological changes occur in the ocular dominance columns of the visual cortex (Chap. 19). An inadequate input to the visual cortex from the macula of the abnormal eye was insufficient during the critical period to nurture the maturation of the experience-dependent synaptic plasticity in the ocular dominance columns. This failure during the critical period results in a permanent amblyopia. Ocular dominance plasticity is one of the best examples of synaptic plasticity in the neocortex.

The concept of critical period during childhood is the basis for the suggestion that young children should be exposed to rich visual experiences, even more than they can handle intelligently. This should help to ensure the optimal maturation of the child's visual pathways.

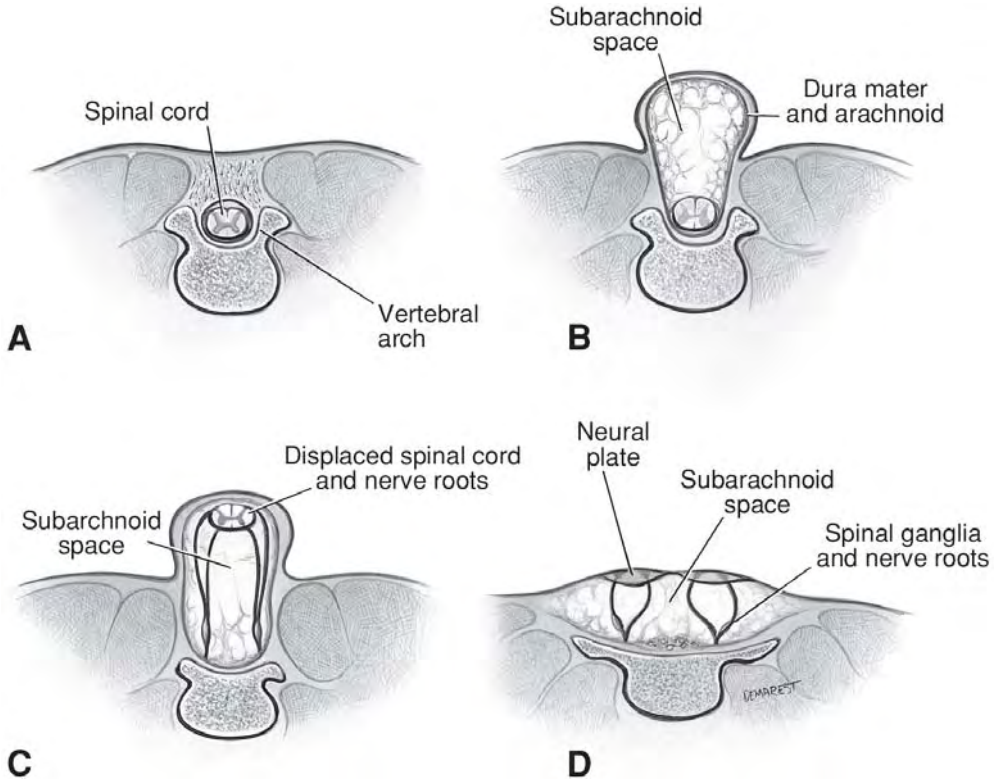


Figure 6.10: Some anomalies that can occur in the lumbosacral region. **(A)** Spina bifida occulta results from the failure of the neural arches of the vertebrae to fuse dorsally. **(B)** Spina bifida with meningocele is a defect with a subarachnoid fluid-filled meningeal cyst bulging through unfused neural arches. The cyst is covered with skin. **(C)** Spina bifida with myelomeningocele is a defect with a meningeal cyst containing spinal cord and nerve roots. **(D)** Spina bifida with myeloschisis is a defect in which the neural plate (having failed to close) is exposed to the surface.

Spina Bifida

Spina bifida is one of the more common defects that occur at spinal cord levels. The term is used to cover a wide range of closure defects, usually located in the lower lumbar region (*see* **Fig. 6.10**). The most extreme version occurs when the neural plate in the lumbar region remains as a plate exposed to the outside. An infant with this defect has bladder and bowel incontinence, sensory loss, and motor paralysis of the lower extremities. In less severe cases, the meninges or the meninges along with the spinal cord, though displaced backward, are still covered by the skin. In a minor form, only the bony neural arches might be defective and functional impairment is absent.

SUGGESTED READINGS

Ambron RT, Dulin MF, Zhang XP, Schmied R, Walters ET. Axoplasm enriched in a protein mobilized by nerve injury induces memory-like alterations in Aplysia neurons. *J. Neurosci.* 1995;15:3440–3446.

Bagri A, Marin O, Plump AS, et al. Slit proteins prevent midline crossing and determine the dorsoventral position of major axonal pathways

in the mammalian forebrain. *Neuron* 2002;33: 233–248.

Barinaga M. Fetal neuron grafts pave the way for stem cell therapies. *Science.* 2000;287: 1421–1422.

Barry MF, Ziff EB. Receptor trafficking and the plasticity of excitatory synapses. *Curr. Opin. Neurobiol.* 2002;12:279–286.

Brose K, Tessier-Lavigne M. Slit proteins: key regulators of axon guidance, axonal branching, and cell migration. *Curr. Opin. Neurobiol.* 2000; 10:95–102.

Cohen-Cory S. The developing synapse: construction and modulation of synaptic structures and circuits. *Science* 2002;298:770–776.

Dickson BJ. Molecular mechanisms of axon guidance. *Science* 2002;298:1959-1964.

Dowling J. *Neurons and Networks: An Introduction to Neuroscience.* Cambridge, MA: Harvard University Press, 1993.

Edgerton V, Bigbee L, deLeon R. Plasticity of the spinal neural circuitry. *Ann. Rev. Neurosci.* 2004; 27:145–167.

Gottlieb DI. Large-scale sources of neural stem cells. *Annu. Rev. Neurosci.* 2002;25:381–407.

Gould E, Gross CG. Neurogenesis in adult mammals: some progress and problems. *J. Neurosci.* 2002;22:619–623.

Gould E, Reeves AJ, Graziano MS, Gross CG. Neurogenesis in the neocortex of adult primates. *Science* 1999;286:548–552.

Gould E, Vail N, Wagers M, Gross CG. Adult-generated hippocampal and neocortical neurons in macaques have a transient existence. *Proc. Natl. Acad. Sci. USA* 2001;98:10,910–10,917.

Hatten ME. Central nervous system neuronal migration. *Annu. Rev. Neurosci.* 1999;22:511–539.

Hatten ME. New directions in neuronal migration. *Science* 2002;297:1660-1663.

Holden C. Stem cell research. Cells find destiny though merger. *Science* 2003;300:35.

Irvine KD, Rauskolb C. Boundaries in development: formation and function. *Annu. Rev. Cell Dev. Biol.* 2001;17:189–214.

Jessell TM, Sanes JR. Development. The decade of the developing brain. *Curr. Opin. Neurobiol.* 2000;10:599–611.

Jones EG. Cortical and subcortical contributions to activity-dependent plasticity in primate somatosensory cortex. *Annu. Rev. Neurosci.* 2000; 23:1–37.

Kozorovitskiy Y, Gould E. *Adult neurogenesis: a mechanism for brain repair? J. Clin. Exp. Neuropsychol.* 2003;25:721–732.

Lyuksyutova AI, Lu CC, Milanesio N, King LA, Guo N, Wang Y, Nathans J, Tessier-Lavigne M, Zou Y. Anterior–posterior guidance of commissural axons by Wnt-frizzled signaling. *Science* 2003;302:1984–1988.

McAllister AK, Katz LC, Lo DC. Neurotrophins and synaptic plasticity. *Annu. Rev. Neurosci.* 1999;22:295–318.

Mueller BK. Growth cone guidance: first steps towards a deeper understanding. *Annu. Rev. Neurosci.* 1999;22:351–388.

Nguyen-Ba-Charvet KT, Picard-Riera N, et al. Multiple roles for slits in the control of cell migration in the rostral migratory stream. *J. Neurosci.* 2004;24:1497–1506.

Nijhawan D, Honarpour N, Wang X. Apoptosis in neural development and disease. *Annu. Rev. Neurosci.* 2000;23:73–87.

Rakic P. Adult neurogenesis in mammals: an identity crisis. *J. Neurosci.* 2002;22:614-618.

Rakic P. Neurogenesis in adult primates. *Prog. Brain Res.* 2002;138:3–14.

Rubenstein JL, Shimamura K, Martinez S, Puelles L. Regionalization of the prosencephalic neural plate. *Annu. Rev. Neurosci.* 1998;21:445–477.

Sanes DH, Reh TA, Harris WA. *Development of the Nervous System.* San Diego, CA: Academic; 2000.

Schnorrer F, Dickson BJ. Axon guidance: morphogens show the way. *Curr. Biol.* 2004;14:R19–R21.

Shirasaki R, Pfaff SL. Transcriptional codes and the control of neuronal identity. *Annu. Rev. Neurosci.* 2002;25:251–281.

Stein E, Tessier-Lavigne M. Hierarchical organization of guidance receptors: silencing of netrin attraction by slit through a Robo/DCC receptor complex. *Science* 2001;291:1928-1938.

Tessier-Lavigne M, Goodman CS. The molecular biology of axon guidance. *Science* 1996; 274:1123–1133.

Weissman IL, Anderson DJ, Gage F. Stem and progenitor cells: origins, phenotypes, lineage commitments, and transdifferentiations. *Annu. Rev. Cell Dev. Biol.* 2001;17:387–403.

Zhang XP, Ambron RT. Positive injury signals induce growth and prolong survival in Aplysia neurons. *J. Neurobiol.* 2000;45:84–94.

Zigova T, Sanberg PR, Sanchez-Ramos J, eds. *Neural Stem Cells: Methods and Protocols.* Totowa, NJ: Humana; 2002.

Zigova T, Snyder E, Sanberg P, eds. *Neural Stem Cells for Brain and Spinal Cord Repair.* Totowa, NJ: Humana; 2003.

Zou Y, Stoeckli E, Chen H, Tessier-Lavigne M. Squeezing axons out of the gray matter: a role for slit and semaphorin proteins from midline and ventral spinal cord. *Cell.* 2000;102:363–375.

7
The Spinal Cord

Anatomic Organization
Spinal Roots and Peripheral Nerves
Laminae of the Spinal Cord
Pathways and Tracts

The spinal cord is a slender cylindrical structure less than 2 cm in diameter composed of gray and white matter that is located in the upper two-thirds of the vertebral canal and is surrounded by the bony vertebral column. It is the central processing and relay station (1) receiving input via peripheral nerves from the body and via descending tracts from the brain and (2) projecting output via the peripheral nerves to the body and via the ascending tracts to the brain.

ANATOMIC ORGANIZATION

The spinal cord extends from the foramen magnum at the base of the skull to a cone-shaped termination, the *conus medullaris*, usually located at the caudal level of the first lumbar centrum. The nonneural *filum terminale* continues caudally as a filament from the conus medullaris to its attachment in the coccyx (*see* **Fig. 5.1**).

Meningeal Coverings

The spinal cord is surrounded by three meninges, which are continuous with those encapsulating the brain (Chap. 5). All three meninges invest the nerve roots emerging from the spinal cord and are continuous with the connective tissue sheath of the peripheral nerves.

The vascular *pia mater* is intimately attached to the spinal cord and its roots. The dura and nonvascular *arachnoid* extends caudally to the sacral-5 vertebral level, where they merge with the filum terminale to form the coccygeal ligament or filum of the dura. The *subarachnoid space*, which is filled with cerebrospinal fluid (CSF) and blood vessels surrounds the spinal cord and is called the *spinal* or *lumbar cistern* between the conus medullaris and the sacral-2 level (*see* **Fig. 5.1**). The roots of the lumbar and sacral spinal nerves "float" within the CSF of this cistern. To avoid injury to the spinal cord during removal of CSF, spinal taps into the cistern are made in the lower lumbar region.

The *dura mater* and the capillary-thin *subdural space* (not containing CSF) surround the arachnoid and merge with the filum terminale at the sacral-2 level. The spinal cord is suspended by a series of 20–22 paired lateral septa of pia mater surrounding the cord extending laterally as flanges through the arachnoid to the dura mater, called the *denticulate ligaments*. The pointed attachment to the dura mater is between two successive spinal nerves. The ligaments are oriented rostrocaudally in a frontal plane between the dorsal and ventral roots.

Between the dura mater (equivalent to inner dura mater surrounding the brain) and the periosteum of the vertebral column (equivalent to outer dura mater surrounding the brain) is the *epidural space* containing venous plexuses and fat. The epidural space caudal to the sacral-2 level is the site for injection of anesthetics used to modify sensory input (e.g., saddle block for painless childbirth).

Blood Supply

The variably sized spinal arteries are branches of the vertebral, cervical, thoracic, and lumbar arteries. Each artery passes through an intervertebral foramen and divides into an anterior and a posterior spinal root (*radicular arteries*), which form an anastomotic plexus on the surface of the spinal cord (*see* **Fig. 12.2**). Venous drainage is via a venous plexus, and veins roughly parallel the arterial tree. The large spinovertebral venous plexus is continuous rostrally with that surrounding the brain. Venous pressure within these veins and CSF pressure can become elevated when the outflow of venous blood into the systemic circulation is impeded, as happens when the pressure in the thoracic and abdominal cavities increases while one is lifting a heavy object or coughing.

SPINAL ROOTS AND PERIPHERAL NERVES

The spinal cord receives input and projects output via nerve fibers in the spinal rootlets and roots, spinal nerves, and their branches (*see* **Figs. 7.1 and 7.2**). Nerve fibers emerge from the spinal cord in an uninterrupted series of dorsal and ventral rootlets that join to form 31 pairs of *dorsal and ventral roots*. In the vicinity of each intervertebral foramen, a dorsal root and a ventral root join to form a *spinal nerve*, which supplies the innervation of a segment of the body. In all, there are 8 pairs of cervical (C), 12 pairs of thoracic (T), 5 pairs of lumbar (L), 5 pairs of sacral (S), and 1 pair of coccygeal (Co) roots and nerves (*see* **Fig. 7.1 and Table 7.1**). Cervical-1 and coccygeal-1 usually have only ventral roots.

Spinal cord segments and their nerves are named after their corresponding vertebrae. Cervical nerves C1 to C7 are numbered for the vertebra just caudal to the foramen through which they pass. In humans, because there are only seven cervical vertebrae, C8 and all other spinal nerves are numbered for the vertebra just rostral. Because the spinal cord is much shorter than the bony vertebral column, the lumbar and sacral nerves develop long roots, which extend as the *cauda equina* (horse's tail) within the spinal cistern (*see* **Figs. 5.1 and 7.1**).

The cord is enlarged in those segments that innervate the upper extremities (called the *cervical [brachial] enlargement*, which extends from C5 to T1 spinal levels) and in those segments that innervate the lower extremities (called the *lumbosacral enlargement*, which extends from L1 to S2).

Functional Components of Spinal Nerves

Each spinal nerve contains nerve fibers classified into one of four functional components, namely (1) *general somatic afferent*, (2) *general visceral afferent*, (3) *general somatic efferent*, and (4) *general visceral efferent*. Components that are distributed throughout the body are designated *general*, whereas those that innervate the body wall and extremities are *somatic* and those that innervate the viscera are *visceral*. Furthermore, sensory fibers are *afferent* and motor fibers are *efferent*.

Dorsal Roots

The *dorsal (sensory) roots* consist of afferent fibers that convey input via spinal nerves from the sensory receptors in the body to the spinal cord (*see* **Fig. 7.2**). The cell bodies of these neurons are located in the *dorsal root ganglia* within the intervertebral foramina.

Table 7.1

Interspace Spinal Process of vertebra	*between vertebral bodies*[a]	*Spinal Cord Segment*
C1	C1–2	
C6	C6	T1
T10	T10	L1
T12	T12	S1
T12–L1	All sacral and coccygeal levels	
S2 or S3	Caudal terminations of subarachnoid space	
Coccyx	Termination of filum terminale	

[a] Named from centrum of vertebra above interspace.

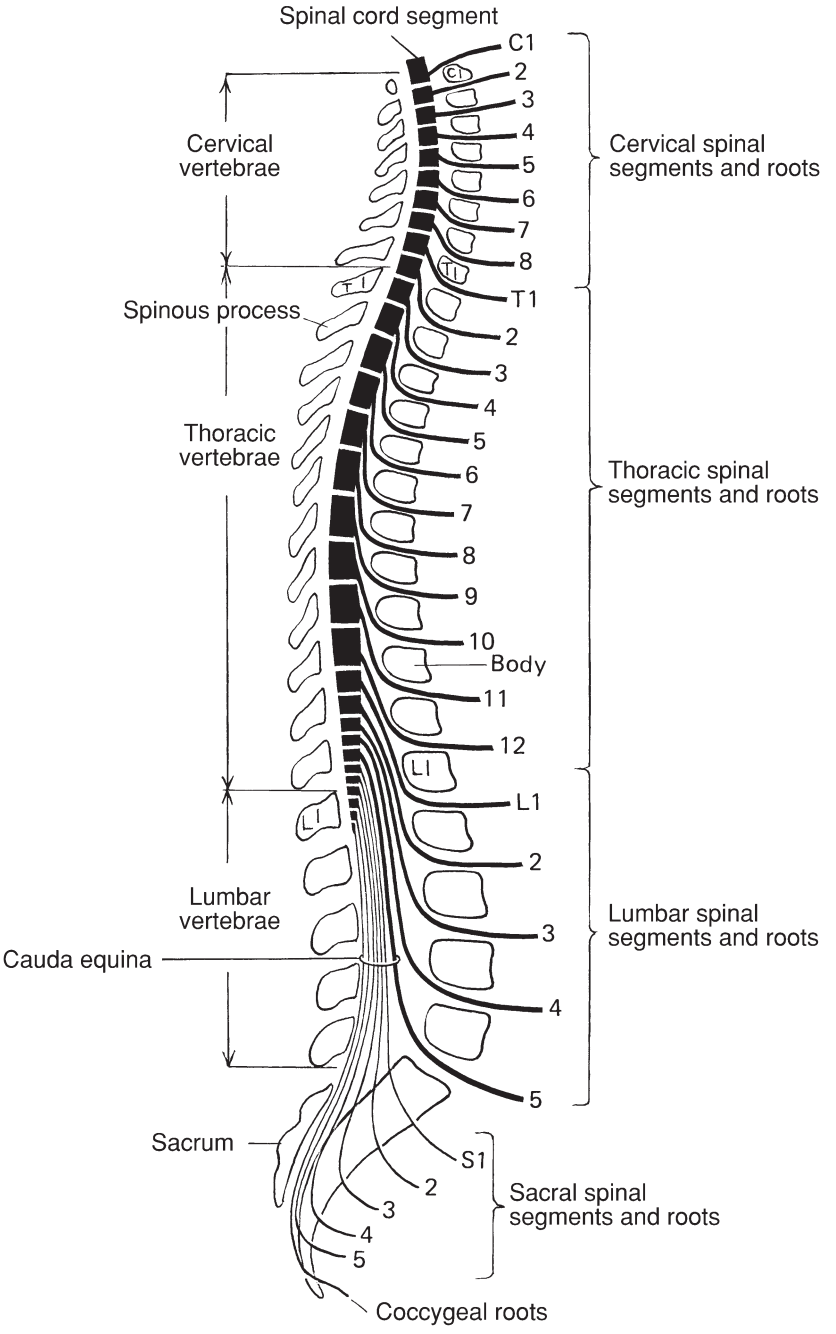


Figure 7.1: Topographic relations of the spinal cord segments, spinous processes, and bodies of the vertebrae, intervertebral foramina, and spinal nerves. Refer to **Table 7.1**. Spinal nerves from cord segments C1–C7 emerge from the spinal canal through the intervertebral foramen immediately above their corresponding vertebrae. Because there are only seven cervical vertebrae, fibers from C8 and all other segments emerge below the corresponding vertebrae.

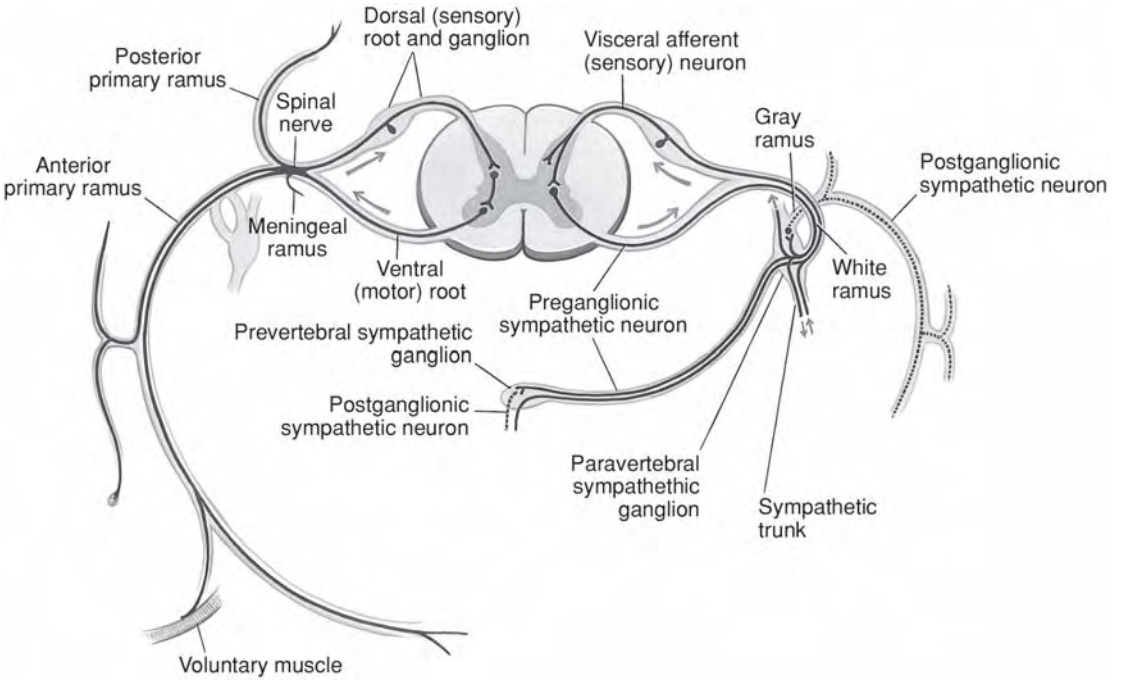


Figure 7.2: Neurons of a reflex arc of the somatic nervous system on the left, and a visceral reflex arc of the sympathetic nervous system on the right. The spinal somatic reflex arcs are described in Chapter 8, and the spinal visceral arcs are described in Chapter 20.

Despite the term, these ganglia contain no synapses. The fibers of the dorsal root of each spinal nerve supply the sensory innervation to a skin segment known as a dermatome (*see* **Fig. 7.3 and Table 7.2**). There is usually no C1 or Co1 *dermatome.* Adjacent dermatomes overlap, so that the loss of one dorsal root results in diminished sensation, not a complete loss, in that dermatome (Chap. 9).

The general afferent fibers are classified into (1) *general somatic afferent (GSA)* fibers, conveying information from sensors in the extremities and body wall, and (2) *general visceral afferent (GVA)* fibers, conveying information from the viscera (e.g., circulatory system).

A classification of sensory receptors and their probable functional roles are presented in **Table 7.3**. Further details concerning sensations, functional significance, reflexes, and pathways associated with these receptors are discussed in subsequent chapters. A classification of afferent fibers by conduction velocity recognizes groups I, II, III, and IV fibers (Chap. 8). Furthermore, group I is subdivided into group Ia, for nerve impulses from the primary sensory endings of muscle spindles, and group Ib, for impulses from Golgi tendon organs (*see* **Table 7.4**). Group II fibers transmit impulses from encapsulated skin and joint receptors (e.g., Meissner's and Pacinian corpuscles), monitoring touch, pressure, temperature, and joint movements, and secondary sensory endings of muscle spindles. Groups III and IV fibers transmit impulses arising from unencapsulated endings, mediating pain, touch, and pressure. In all cases, fibers of greater diameter have a higher conduction velocity than thinner fibers, and myelinated fibers are faster than unmyelinated ones.

A second classification of fibers by conduction velocity into A, B, and C is also employed, for both sensory and motor fibers. The A and B

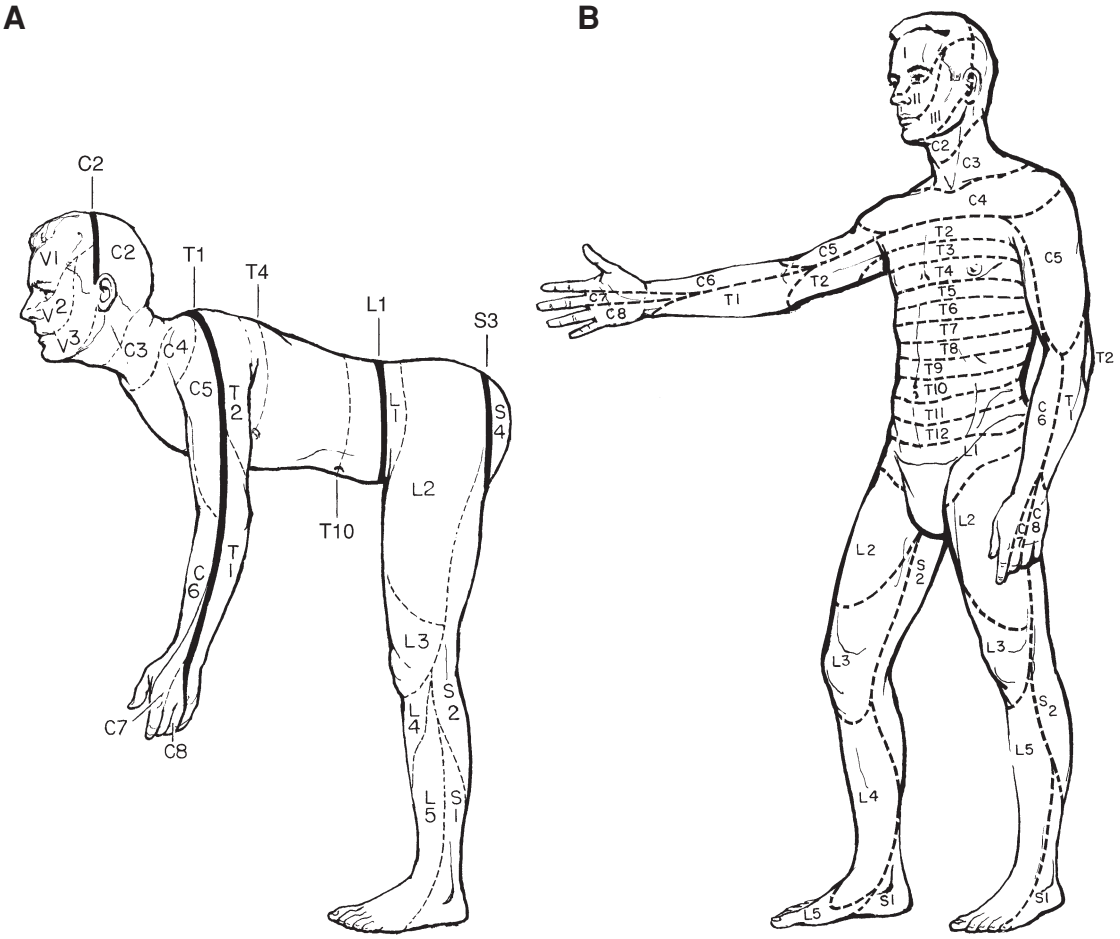


Figure 7.3: Dermatomal (segmental) innervation of the skin. Refer to **Table 7.2**. The trigeminal nerve has three dermatomes: ophthalmic division (V1), maxillary division (V2), and mandibular division (V3).

fibers are myelinated and the C fibers are unmyelinated. The A fibers are further divided by conduction velocity (hence, fiber size) into alpha, beta, gamma, and delta (*see* **Table 7.4**).

Ventral Roots

The ventral (motor) roots consist of efferent fibers that convey output from the spinal cord. There are two functional components: (1) *general somatic efferent (GSE) fibers,* which innervate voluntary striated muscles, and (2) *general visceral efferent (GVE) fibers,* which convey influences to the involuntary smooth muscles, cardiac muscle, and glands (*see* **Table 7.4**).

Table 7.2

Dorsal spinal root	*Body region innervated*[a]
C2	Occiput
C4	Neck and upper shoulder
T1	Upper thorax and inner side of arm
T4	Nipple zone
T10	Umbilical girdle zone
L1	Inguinal region
L4	Great toe, lateral thigh, and medial leg
S3	Medial thigh
S5	Perianal region

[a] Dermatome and region to which radicular parts is referred.

Table 7.3: Classification of Sensory Receptors (Probable Functional Roles)

I. Receptors of general sensibility (exteroceptive)
  A. Endings in epidermis
    1. Free nerve endings (tactile, pain, thermal sense)
    2. Terminal disks of Merkel (tactile)
    3. Nerve (peritrichial) endings in hair follicle (tactile, movement detector)
  B. Endings in connective tissues (skin and connective tissue throughout body)
    1. Free nerve endings (pain, thermal sense)
    2. Encapsulated nerve endings
      a. End bulbs of Ruffini (touch-pressure, position sense, kinesthesia)
      b. Corpuscles of Meissner (tactile, flutter sense)
      c. Corpuscles of Pacini (vibratory sense, touch-pressure)
  C. Endings in muscles, tendons, and joints (proprioceptive)
    1. Neuromuscular spindles (stretch receptors)
    2. Golgi tendon organs, neurotendinous endings (tension receptors)
    3. End bulbs of Ruffini in joint capsule (touch-pressure, position sense, kinesthesia)
    4. Corpuscles of Pacini (touch-pressure, vibratory sense, kinesthesia)
    5. Free nerve endings (pain)

II. Receptors of special senses
  A. Bipolar neurons, of olfactory mucosa (olfaction)
  B. Taste buds (gustatory sense)
  C. Rods and cones in retina (vision)
  D. Hair cells in spiral organ of Corti (audition)
  E. Hair cells in semicircular canals, saccule, and utricle (equilibrium, vestibular sense)

III. Special receptors in viscera (interoceptive)
  A. Pressoreceptors in carotid sinus and aortic arch (monitor arterial pressure)
  B. Chemoreceptors in carotid and aortic bodies and in or on surface of medulla (monitor arterial oxygen and carbon dioxide levels)
  C. Chemoreceptors probably located in supraoptic nucleus of hypothalamus (monitor osmolarity of blood)
  D. Free nerve endings in viscera (pain, fullness)
  E. Receptors in lungs (respiratory and cough reflexes)

These fibers are axons of (1) *alpha motoneurons* (*lower motoneurons*; Chap. 11) that convey impulses to the motor end plates of voluntary muscle fibers, (2) *gamma motoneurons* that convey impulses to the motor endings of intrafusal fibers of muscle spindles (Chap. 8), and (3) *preganglionic (lightly myelinated) autonomic neurons* that synapse with postganglionic (unmyelinated) neurons (Chap. 20). Gamma motoneurons are also known as *fusimotor neurons* (innervate the muscles of the fusiform-shaped spindles).

The muscles innervated by motoneurons from a single spinal cord segment constitute a *myotome*. Like dermatomes, there is myotomal overlap. The spinal cord innervation of a few muscles and regions is shown in **Table 7.5**. A single alpha motoneuron together with the muscle fibers it innervates constitutes a *motor unit*. Such units vary widely in the number of muscle fibers they contain, ranging from units innervating 3 to 8 muscle fibers in the small finely controlled extraocular muscles of the eye or those in the larynx important for speech, to units containing as many as 2000 muscle fibers in postural muscles (e.g., soleus in the leg). Individual muscle fibers are innervated by one motor end plate, referred to as a *neuromuscular junction*, usually located near the middle of the cell. The muscle fibers of a motor unit intermingle with those from other motor units.

In general, there is a continuum of attributes that form three functional types of muscle fiber, namely (1) slow-twitch fibers, (2) fast-fatigable-twitch fibers, and (3) fast-fatigue-resistant twitch fibers. Each motor unit comprises only one type. The *slow-twitch fibers* are the signatures of "red meat" muscles that have (1) a rich extracellular matrix of blood capillaries, (2) numerous mitochondria with high levels of oxidative enzymes, and (3) a large amount of myoglobin that helps absorb and store oxygen from the blood. These are slow-twitch fibers because the force they produce in response to an action potential rises and falls relatively slowly. Their fatigue resistance results from a reliance on oxidation catabolism, whereby glucose and oxygen from the blood is available to

Table 7.4: Classification of Nerve Fibers

Fibers	*Diameters*	*Conduction velocity (m/s)*	*Role/receptors innervated*
		Sensory[a]	
Ia (A-α)	12–20	70–120	Primary afferents of muscle spindle
Ib (A-α)	12–20	70–120	Golgi tendon organ Touch and pressure receptors
II (A-β)	5–14	30–70	Secondary afferents of muscle spindle Touch, pressure, and pacinian vibratory sense receptors
III (A-δ)	2–7	12–30	Touch and pressure receptors Pain and temperature receptors
IV (C)	0.5–1	0.5–2	Pain and temperature receptors Unmyelinated fibers
		Motor[b]	
Alplia (A-α)	12–20	15–120	Alpha motoneurons innervating extrafusal muscle fibers in lamina[a]
Gamma (A-γ)	2–10	10–45	Gamma motoneurons innervating intrafusal muscle fibers in lamina[a]
Preganglionic autonomic fibers (B)	>3	3–15	Lightly myelinated preganglionic autonomic fibers
Postganglionic autonomic fibers (C)	1	2	Unmyelinated postganglionic autonomic fibers

[a] The fibers of I, II, and III are myelinated and those of IV are unmyelinated. The fibers of I and II are associated with mechanoreceptors and those of III with mechanoreceptors in hair skin.

[b] Cell bodies of alpha and gamma motoneurons are located in lamina IX.

[c] A lower motoneuron (lower motor neuron, alpha motoneuron, gamma motoneuron) is a motor neuron with its cell body in the CNS and an axon that innervates voluntary (striated, skeletal) muscle fibers.

regenerate ATP, which fuels the contractile process. The two subtypes of *fast-twitch fibers* comprise most of the "white meat" muscles, characterized by a more rapid rise and fall of their force response. They also tend to have a different form of myosin that possesses cross-bridges and produce force more effectively in rapid shortening velocities. One subtype of the *fast-fatigable-twitch fibers* relies almost exclusively on anaerobic catabolism and has relatively large stores of glycogen. This provides energy to rapidly rephosphorylate ADP, as glycogen is converted to lactic acid. This source is depleted fairly quickly and full recovery could take hours. The second subtype of *fast-fatigue-resistant fibers* combines relatively fast-twitch dynamics and contractile velocity with enough capability to resist fatigue for minutes to hours. World-class sprinters and high jumpers, requiring quick starts and short bursts of speed, could have up to 85% fast-twitch fibers in certain muscles. Fibers of the slow motor units contract and relax relatively slowly and tend to fatigue less rapidly. World-class long-distance runners, especially marathoners, could have up to 90% slow-twitch

Table 7.5

Ventral spinal root	*Muscles innervated*
C5–6	Biceps brachii (flexes elbow)
C6–8	Triceps brachii (extends elbow)
T1–8	Thoracic musculature
T6–12	Abdominal musculature
L2–4	Quadriceps femoris (knee jerk, patellar tendon reflex)
L5–S1–2	Gastrocnemius (ankle jerk, Achilles tendon reflex)

fibers in certain muscles. They display a great capacity for running through fatigue.

LAMINAE OF THE SPINAL CORD

The spinal cord is divided into gray matter (cell bodies, dendrites, axons, and glial cells) and white matter (myelinated and unmyelinated axons and glial cells). The nerve fibers within the gray matter are oriented in the transverse plane, whereas those of the white matter are oriented in the longitudinal plane parallel to the neuraxis. The gray matter has been parceled anatomically, primarily on the basis of the microscopic appearance, into nuclei that conform to a laminar pattern (*Rexed's laminae*) (*see* **Figs. 7.4, 7.5, and Table 7.6**). The gray matter is also divided into a *posterior horn* (laminae I–VI), an intermediate zone (lamina VII and X), and an *anterior horn* (laminae VIII and IX). The white matter is divided into three columns (*funiculi*): posterior, lateral, and anterior (*see* **Fig. 7.5**).

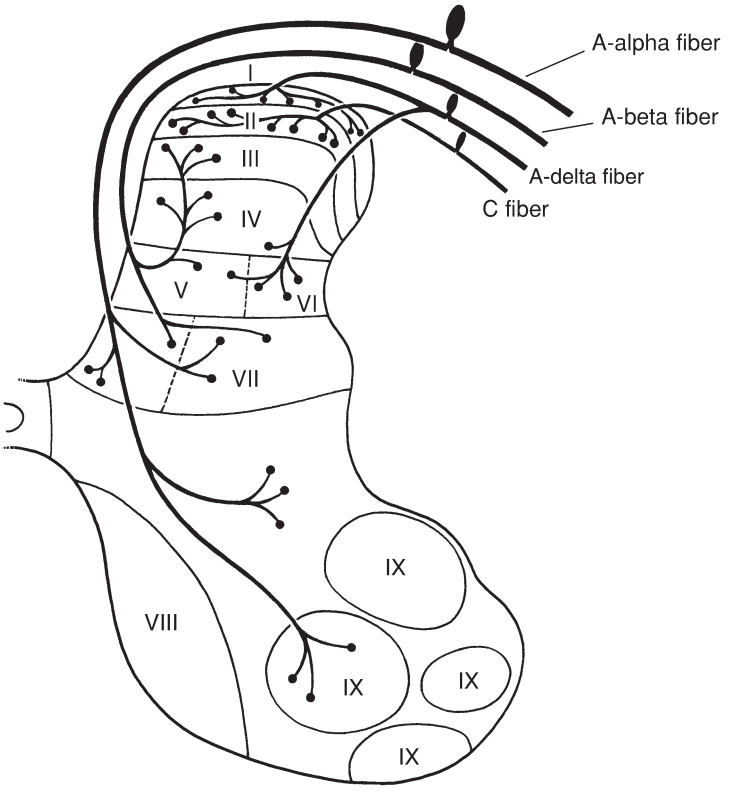


Figure 7.4: The sensory fibers of the dorsal root and the laminae of the spinal cord in which each type terminates. The heavily myelinated A alpha fibers from neuromuscular spindles and Golgi tendon organs terminate in laminae VI, VII, and IX (Chap. 8). The myelinated A beta fibers from cutaneous mechanoreceptors terminate in laminae III–VI (Chap. 10). The thinly myelinated and unmyelinated A delta and C fibers from nociceptors terminate in laminae I–V (Chap. 9). (Adapted from Brodal.)

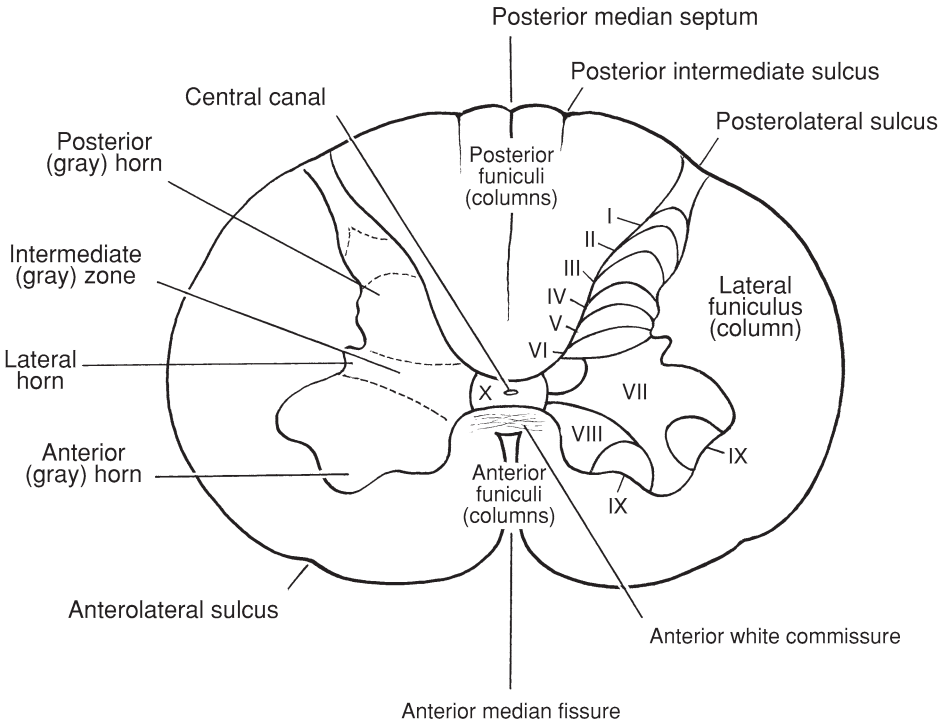


Figure 7.5: Section through a cervical level of the spinal cord to illustrate some subdivisions of the gray matter and white matter. The white matter is composed of three funiculi (columns). The gray matter is divided into two horns and an intermediate zone. Division of the gray matter into Rexed's laminae is shown on the right.

PATHWAYS AND TRACTS

Sensory signals originating in sensory receptors in the body and limbs are transmitted through the spinal cord to the brain along sensory pathways. Motor commands from the higher centers in the brain descend through the spinal cord along motor pathways. Within the white matter of the spinal cord, the sensory fibers of the pathways form groups called *ascending tracts* or *fasciculi,* and fibers of the motor pathways form groups referred to as *descending tracts* (*see* **Fig. 7.6**). The functional significance and location of these pathways form a basis of neurologic diagnosis. Lesions within or impinging upon the nervous system often are revealed by alterations in sensory

Table 7.6

Lamina	*Corresponding nucleus*
I	Posteromarginal nucleus
II	Substantia gelatinosa
III and IV	Proper sensory nucleus (nucleus proprius)
V	Zone anterior to lamina IV
VI	Zone at base of posterior horn
VII	Zona intermedia (includes intermediomedial and intermediolateral nuclei, dorsal nucleus of Clarke, and sacral autonomic nuclei)
VIII	Zone in anterior horn (restricted to medial aspect in cervical and lumbosacral enlargements)
IX	Medial nuclear column and lateral nuclear column

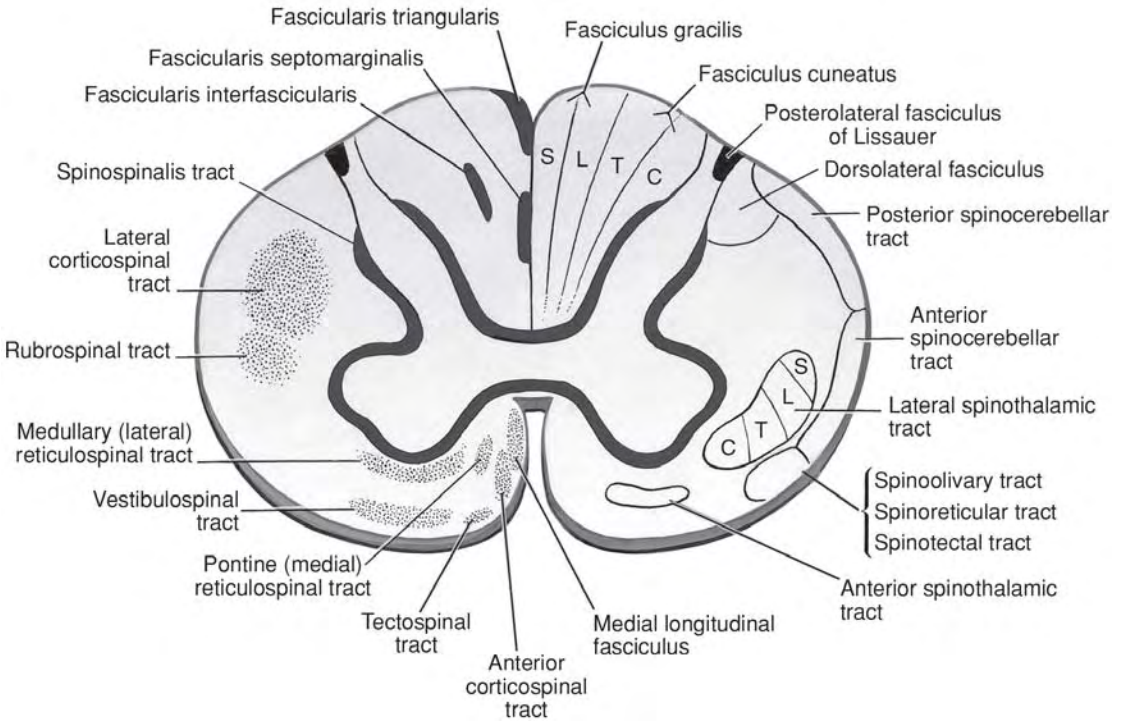


Figure 7.6: The spinal cord tracts. The ascending tracts are represented as plain outlines on the right, the descending tracts as stippled outlines on the left, and the intrinsic spinal tracts (composed of descending and/or ascending fibers) as solid outlines. The representation of the tracts is arbitrarily drawn. The lamination of the posterior columns and lateral spinothalamic tracts is indicated: C, cervical; T, thoracic; L, lumbar; S, sacral.

perceptions, balance, movement, or reflex activity, and the site often can be pinpointed by the examiner who has a thorough knowledge of these tracts and the associated roots of the spinal nerves.

Interposed between the afferent neurons of the dorsal roots and the efferent neurons of the ventral roots within the gray matter of the spinal cord are spinal interneurons that send their axons (crossed and uncrossed) to higher and lower segmental levels for the execution of various spinal intersegmental reflexes. These axons (1) ascend and descend to form columns in the white matter adjacent to the gray matter (black band in **Fig. 7.6**), (2) originate and terminate within the spinal cord, and (3) functional connect the various spinal levels. The columns are called the *spinospinal fasciculi* or *fasciculi proprii* of the spinal cord. The axons of these fasciculi are linked with the spinoreticular tract, which goes to the brainstem as the spinoreticulothalamic pathway (Chap. 22).

Regional differences are present at various levels of the spinal cord (*see* **Fig. 7.7**). The amount of gray matter at any spinal level is primarily related to the richness of the peripheral innervation. Hence, the gray matter is largest in the spinal segments of the cervical and lumbosacral enlargements innervating the upper and lower extremities; such large structures require a massive innervation. The tho-

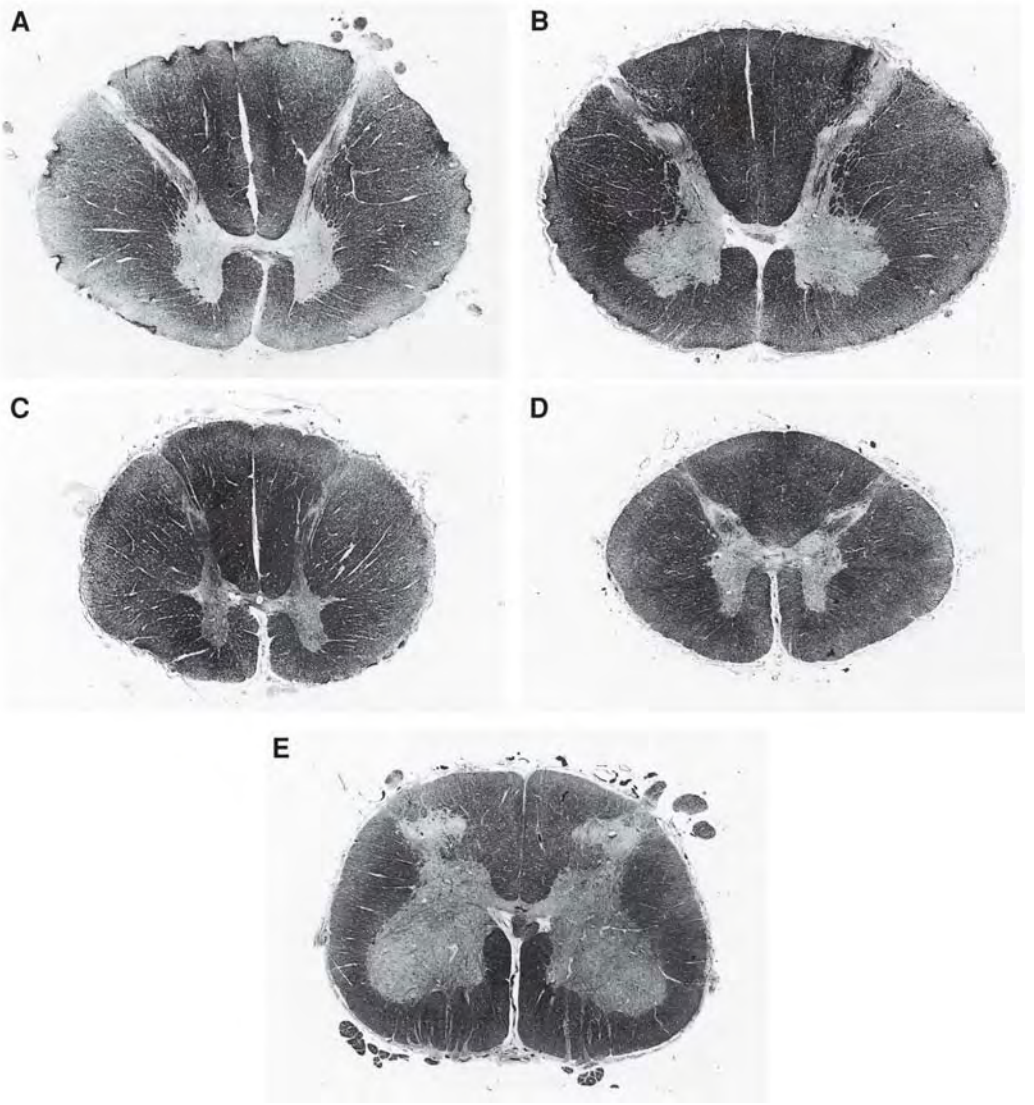


Figure 7.7: Representative sections from several levels of the adult human spinal cord. **(A)** High cervical level; **(B)** cervical enlargement level; **(C)** midthoracic level; **(D)** low thoracic level; **(E)** lumbar level. All photographs of these Weigert-stained sections are at the same magnification. (Courtesy of Dr. Joyce Shriver, Mount Sinai School of Medicine.)

racic and upper lumbar levels have relatively small amounts of gray matter: They innervate the thoracic and abdominal regions.

The absolute number of nerve fibers in the white matter increases at each successive higher spinal level. Stated otherwise, the white matter of a spinal level caudal to another level has fewer fibers. The difference occurs because (1) additional fibers of the ascending sensory pathways join the white matter at each successive higher level and (2) fibers of the descending motor pathways from the brain leave the white matter before terminating in the gray matter at each successive level.

SUGGESTED READINGS

Abdel-Maguid TE, Bowsher D. 1984. Interneurons and proprioneurons in the adult human spinal grey matter and in the general somatic and visceral afferent cranial nerve nuclei. *J. Anat.* 139(Pt. 1):9-19.

Bowsher D, Abdel-Maguid TE. Superficial dorsal horn of the adult human spinal cord. *Neurosurgery.* 1984;15:893-899.

Boyd IA, Davey MR. *Composition of Peripheral Nerves.* Edinburgh: Livingstone; 1968.

Brodal A. *Neurological Anatomy in Relation to Clinical Medicine,* 3rd ed. New York: Oxford University Press; 1981.

Brown MC, Hopkins WG, Keynes RJ, Hopkins WG. *Essentials of Neural Development.* New York: Cambridge University Press; 1991.

Coggeshall RE. Law of separation of function of the spinal roots. *Physiol. Rev.* 1980;60:716-755.

Crock HV. *Atlas of Vascular Anatomy of the Skeleton and Spinal Cord.* London: Martin Dunitz; 1996.

Crock HV, Yoshizawa H. *The Blood Supply of the Vertebral Column and Spinal Cord in Man.* New York: Springer-Verlag; 1977.

Crock HV, Yamagishi M, Crock MC. *The Conus Medullaris and Cauda Equina in Man: An Atlas of the Arteries and Veins.* New York: Springer-Verlag; 1986.

Hopkins WG, Brown MC. *Development of Nerve Cells and Their Connections.* New York: Cambridge University Press; 1984.

Landon DN. *The Peripheral Nerve.* New York: Wiley; 1976.

Schiebel A. The organization of the spinal cord**.** In: Davidoff RA ed. *Handbook of the Spinal Cord.* New York: Dekker; 1984: vol. 2.

8
Reflexes and Muscle Tone

Organization of the Somatic Motor (Efferent) System
Spinal Reflex Arcs
Muscle Spindles
Stretch (Myotatic, Deep Tendon) Reflex
Gamma Reflex Loop
Golgi Tendon Organ and Reflex Loop
Flexor Reflexes
Muscle Tone (Tonus)
Coactivation
Integration of Spinal Reflexes: Role of Interneurons

The spinal cord contains the local neuronal circuits that coordinate somatic reflexes. These circuits are participants in the complex voluntary movements of the body that are governed by the higher centers of the brain. One expression of somatic motor function is the effortless ease with which humans carry out the most dexterous of motor activities without a conscious awareness of joint movements and the accompanying muscle contractions synchronized with the required "relaxing" of antagonistic muscles. The quality of sequential combinations of movements is dependent on the continuous flow of visual, somatosensory, and postural (vestibular and joint senses) information that results in seemingly immediate integrated responsive actions. Although we might be consciously aware of making decisions regarding execution of the movements to accomplish the goal, we are unaware of the details that are instrumental in creating the motions, as they seem to take place automatically.

Somatic reflexes are the automatic stereotypic motor responses by voluntary muscles to adequate sensory stimuli. From a vast array of external and internal stimuli bombarding the body, selections are made by sensory receptors within the skin, voluntary muscles, tendons, and joints. From them, a continuous flow of sensory messages is transmitted via spinal and cranial sensory nerves to the spinal cord and brainstem for processing in order to achieve response goals. These are realized by information conveyed via *alpha motoneurons* to the extrafusal muscle fibers and via *gamma motoneurons* to the intrafusal muscle fibers (*see* later). The alpha and gamma motoneurons, called *lower motoneurons*, comprise the *final common pathway* that controls skeletal muscle activities expressed as reflex, postural, rhythmic, and voluntary movements.

The motor apparatus consists of a mechanical arrangement of muscles, bones, and joints organized as levers. Each movement at a joint involves the interplay between agonist muscles and antagonist muscles (including accessory muscles for adjustments). The agonist muscles execute the prime movement and the antagonist muscles counterbalance agonists. The antagonist muscles are involved in decelerating and stabilizing the movement. The *spinal reflex responses*, such as the withdrawal of the upper limb when the finger contacts a hot stove, are

automatic reactions to stimuli involving a simple, neural sequence of a receptor, sensory neurons, interneurons, lower motor neurons, and voluntary muscles. *Posture* is essential as a foundation for the performance of other movements. This positioning and orientation of the body in space is sustained by the constant compensatory adjustments by the musculature in response to shifts in gravity. *Rhythmic patterned motor movements* such as walking, running, and chewing, once voluntarily initiated, continue to be executed automatically. They combine voluntary and reflex activity. The *voluntary movements* initiated in the highest centers in the brain utilize the above-stated movements to express the goals of the skilled volitional actions. These are learned, mastered, honed, and sustained by various amounts of practice. Included are playing a musical instrument, using a word processor, driving a car, riding a bicycle, and participating in such sports as golf, fly casting, and baseball. The proprioceptive receptors are the essential sensors generating a continuous flow of critical information that enables the central nervous system to activate the exquisite coordination of the body musculature required for these reflexes and movements.

Proprioception includes the information sensed by low-threshold mechanoreceptors of the musculoskeletal system comprising muscles, tendons, joint capsules, and ligaments. Their activity results in sensing of the position and movements of the limbs, head, jaws, and back. Its two submodalities are sense of stationary position (*position sense*) and sense of movement (*kinesthesia or kinesthetic sense*). The peripheral receptors signaling these senses include (1) neuromuscular spindles (stretch receptors in muscle) and Golgi tendon organs (tension receptors in tendons), (2) mechanoreceptors in joint capsules, and (3) some cutaneous mechanoreceptors (Chap. 10). The information sensed by these somatic receptors is integrated into spinal reflexes and muscle tone involving the voluntary muscles. This also applies to these activities associated with somatic cranial nerves and the brainstem (jaw reflex, Chap. 10). The *conscious senses* of *position sense* and *kinesthesia* are conveyed via labeled lines of the dorsal column–medial lemniscus system. The *unconscious sense* of *proprioception* is conveyed via the spinocerebellar tracts to the cerebellum (Chap. 10).

ORGANIZATION OF THE SOMATIC MOTOR (EFFERENT) SYSTEM

The somatic nervous system can be conceptualized as a complex integrated assemblage of neural circuits functioning to regulate the activity of the voluntary muscles—those that primarily act through levers of bones and joints. It is only by influencing muscles to contract (or to relax) that the somatic nervous system can express itself. These influences are made manifest through postures and movements. Postures are the body poses from which each movement begins and ends. Each posture is maintained and controlled through a series of reflexes and reactions that utilize continuously acting feedback circuits operating through several segmental levels of control. The flow of voluntary muscle activity from one posture to another posture is a movement. In this context, posture is the framework for a movement, whether crude, stereotyped, skilled, or volitional.

The motor systems within the central nervous system (CNS) are hierarchically organized into the (1) spinal cord, (2) brainstem, and (3) cerebral cortical levels. The *spinal cord level* is involved in automatic and stereotypic responses to peripheral stimuli—known as *reflex responses*. Reflex activity can be modulated from higher levels—that is, either enhanced by excitatory influences or suppressed by inhibitory influences. The *brainstem level* includes the nuclei of origin and their descending motor pathways that project to modulate the motor activity of the spinal cord reflex circuits (Chap. 11). Brainstem centers process neural signals from the cerebral cortex, spinal cord, and cranial nerves (particularly the vestibular nerve). They are integrated into the motor systems projecting to the spinal cord,

which include the corticoreticulospinal pathways, corticorubrospinal pathway, vestibulospinal pathways, corticotectospinal pathway, and raphe–spinal and ceruleus–spinal projections. The *cerebral cortical level* comprises the motor areas, from which, in addition to those mentioned, originate the corticobulbar and the corticospinal tracts (Chaps. 11 and 25). From this level, motor commands stimulate nuclei in the brainstem and spinal cord that activate skilled movements such as speech and writing.

The basal ganglia and cerebellum are major neural structures that participate in modulating the activity of the motor systems. The basal ganglia are specifically involved with movements formulated at the cortical level, including planning of synergies among the muscles during movements (Chap. 24). The basal ganglia receive influences from all neocortical areas and, following processing, send their output back to the motor and premotor cortical areas. The cerebellum has a critical role in acting as a modulator during ongoing motor activity in coordinating the sequence and strength of muscular contractions (Chap. 18).

SPINAL REFLEX ARCS

Reflex responses are mediated by neuronal linkages called *reflex arcs* or *loops*. The structure of a spinal somatic reflex arc can be summarized in the following manner. (1) A sensory receptor responds to an environmental stimulus. (2) An afferent fiber conveys signals through the peripheral nerves to the gray matter of the spinal cord. (3a) In the simplest reflex arc, the afferent root enters the spinal cord and synapses directly with lower motoneurons (*monosynaptic reflex*; *see* **Fig. 8.1**). (3b) In more complex, and more common, reflex arcs, the afferent root synapses with interneurons, which, in turn, synapse with lower motoneurons (polysynaptic reflex; *see* **Figs. 8.1 and 8.2**). (4) A lower motoneuron transmits impulses to effectors—striated voluntary (skeletal) muscles. Spinal reflexes are also classified as (1) segmental, (2) intersegmental, or (3) suprasegmental reflexes. A *segmental reflex* comprises neurons associated with one or even a few spinal segments. An *intersegmental reflex* consists of neurons associated with several to many spinal segments. A *suprasegmental reflex* involves neurons in the brain that influence the reflex activity in the spinal cord.

Reflexes in which the sensory receptor is in the muscle spindle of any muscle group are known as *myotatic*, *stretch*, or *deep tendon reflexes* (DTR). These are intrasegmental reflexes. Examples are (1) the biceps reflex—tapping the biceps brachii tendon results in flexion of the forearm at the elbow, (2) the triceps reflex—tapping the triceps tendon results in extension of the forearm at the elbow, (3) the quadriceps reflex (knee jerk—tapping of the quadriceps tendon results in extension of the leg at the knee, and (4) the triceps sural reflex (ankle jerk)—tapping of the Achilles tendon results in plantar flexion of the foot.

Reflexes in which the sensory receptor is the Golgi tendon organ (GTO), located in a tendon at its junction with a muscle, are known as *Golgi tendon reflexes* (*see* **Fig. 8.1**).

A third kind of reflex, with sensory receptors variously located, is a *flexor reflex* (*see* **Fig. 8.2**). In this reflex, for example, the upper extremity withdraws from a noxious stimulus such as a hot stove. The reflex comprises (1) sensory receptors, (2) afferent neurons, (3) spinal interneurons, (4) alpha motoneurons, and (5) voluntary muscles. The flexor reflex is a protective reflex initiated by a diverse group of receptors in the skin, muscles, joints, and viscera and conveyed by A-delta and C pain fibers, as well as group III and IV fibers (called flexor reflex afferents [FRA]s). Intense stimulation can elevate the level of excitability within the spinal cord to a point at which a *crossed reflex* is evoked, with such responses as leaning or jumping away from a stimulus (*see* **Fig. 8.3**).

MUSCLE SPINDLES

A *muscle spindle (neuromuscular spindle)* is a 3- to 4-mm-long spindle-shaped (fusiform)

receptor consisting of a capsule encasing 2–12 modified striated muscle fibers known as *intrafusal fibers* (*see* **Fig. 8.4**). The spindles are oriented in parallel with the skeletal *extrafusal fibers*, so designated because of their location outside the spindles. Extrafusal fibers are the voluntary muscles that perform the work of contraction. The capsule of the spindle is continuous with the connective tissue between the extrafusal fibers and with the tendon of the muscle.

Muscle spindles are sensory receptors that monitor the length and rate of change in length of the extrafusal fibers and, thus, are called *stretch receptors*. They have both a motor and a sensory innervation. The motor innervation of the intrafusal fibers is by *gamma motoneurons (fusimotor neurons)* and the extrafusal fibers by the *alpha motoneurons*. The sensory innervation of the intrafusal fibers is by group Ia fibers and group II fibers. Alpha motoneurons and gamma motoneurons are also called lower motoneurons.

Three types of intrafusal fiber are located within a muscle spindle: (1) dynamic nuclear bag fibers, (2) static nuclear bag fibers, and (3) nuclear chain fibers (*see* **Fig. 8.4**). Each fiber is a specialized muscle fiber with a central region that is not contractile. Bag fibers are relatively long and large, with each containing numerous nuclei in a central enlargement or bag (hence, bag fibers). Chain fibers are thinner and

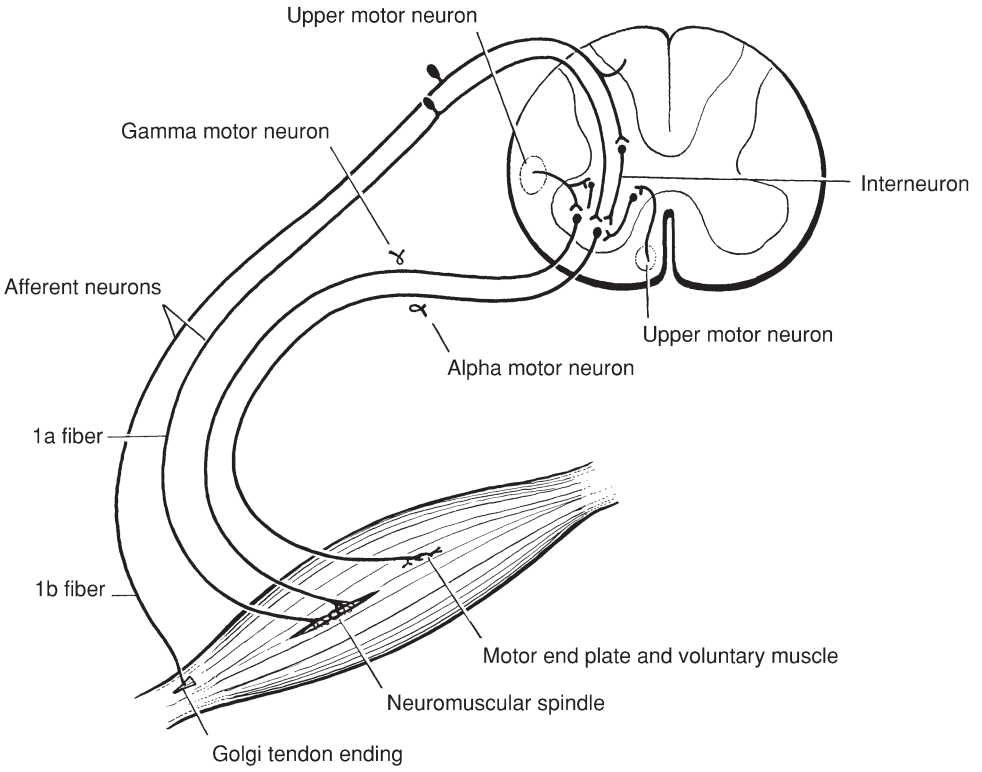


Figure 8.1: Three types of reflex loops are illustrated. (1) The myotatic reflex loop consists of a muscle spindle, Ia afferent neuron, alpha motoneuron, and voluntary muscle fiber. (2) The gamma reflex loop consists of the sequence gamma motoneuron, muscle spindle, Ia afferent neuron, alpha motoneuron, and voluntary muscle fiber. (3) The Golgi tendon organ loop consists of the sequence Golgi tendon organ, Ib afferent neuron, spinal interneuron, alpha motoneuron, and voluntary muscle fiber.

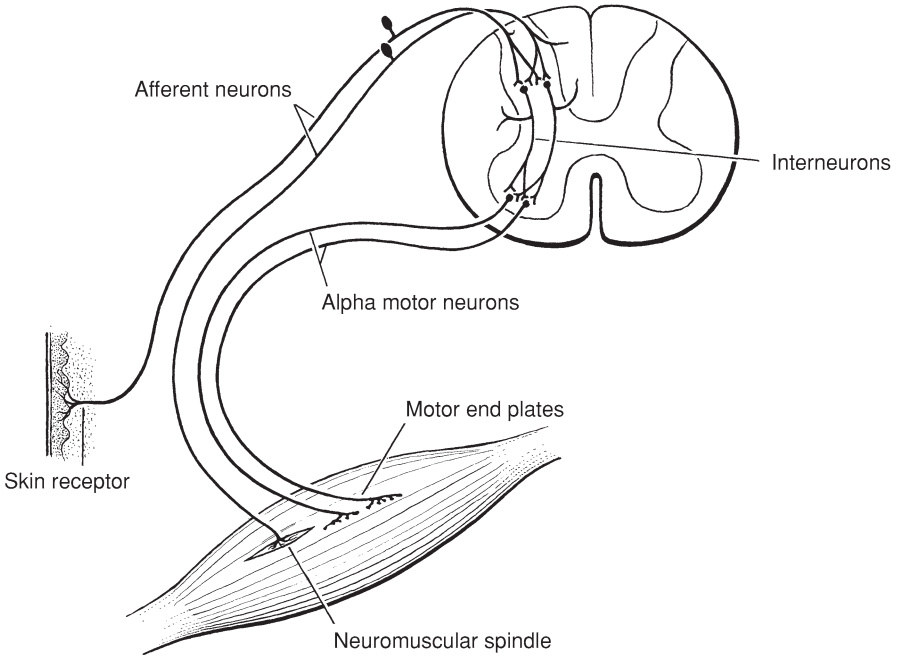


Figure 8.2: The flexor (withdrawal) reflex. This loop consists of the sequence skin receptor, afferent neuron, spinal interneuron, alpha motoneuron and voluntary muscle fiber.

shorter, with each containing a row of nuclei in the central region resembling a chain (hence, chain fibers). The nuclear bag fibers apparently account for the dynamic sensitivity of the primary sensory endings, whereas the nuclear chain fibers account for the static sensitivity of both the primary and secondary sensory endings.

The sensory endings are associated with the central regions of the intrafusal fibers and are responsive to stretching of these muscle fibers. The gamma motor neurons innervate the contractile polar regions of the intrafusal fibers. Contractions of intrafusal fibers tug at the central noncontractile central region from both ends and thus increase the sensitivity of the sensory endings to stretch.

The spindles are innervated by two types of sensory ending: (1) *primary* or *annulospiral endings* derived from group Ia fibers and (2) *secondary* or *flower-spray endings* derived from group II fibers (*see* **Fig. 8.4**). The primary endings terminate as spiral endings on the bag region of the bag fibers and the equatorial region of the chain fibers. The secondary endings terminate as a spray (flower-spray endings) on either side of the primary endings on both types of fiber (*see* **Fig. 8.2**). Gamma motoneurons terminate on the bag and chain fibers as *plate endings* (motor end plates) and *trail endings*. Plate endings terminate primarily on the bag fibers and infrequently on the chain fibers. Trail endings also terminate on both fiber types but primarily in the chain fibers.

Group Ia afferent nerve fibers innervate all three types of intrafusal muscle fiber where they form primary endings. They are the largest-diameter fibers and, hence, the fastest conducting in the peripheral nervous system. Group II afferent (small myelinated) nerve fibers innervate both chain and bag fibers to form secondary endings. The gamma motoneurons and their axons enable the CNS to control the sensitivity of the muscle spindles to length and changes in length. Two types of gamma motor neuron innervate the three types of intra-

fusal fiber. (1) Dynamic gamma motoneurons only innervate dynamic bag fibers. This type increases the dynamic sensitivity of the muscle spindle (gamma dynamic). This is important in reacting to external forces that upset body balance and ongoing movements. (2) Static gamma motoneurons innervate combinations of static bag fibers and chain fibers. The static motoneurons act to increase the static sensitivity of the muscle spindle (gamma static). This acts to increase the firing rate of the afferent fibers to the muscle spindle during constant and maintained muscle length.

Muscle spindles are specialized to sense muscle length and the velocity of change in muscle length. Thus, spindles are stretch-gated receptors that respond to muscle stretch. In contrast, Golgi tendon organs (GTO) of a muscle tendon are tension-gated receptors that respond to muscle tension (*see* **Fig. 8.5**).

Upon entering the spinal cord, the Ia afferents in the dorsal root bifurcate. The main axon

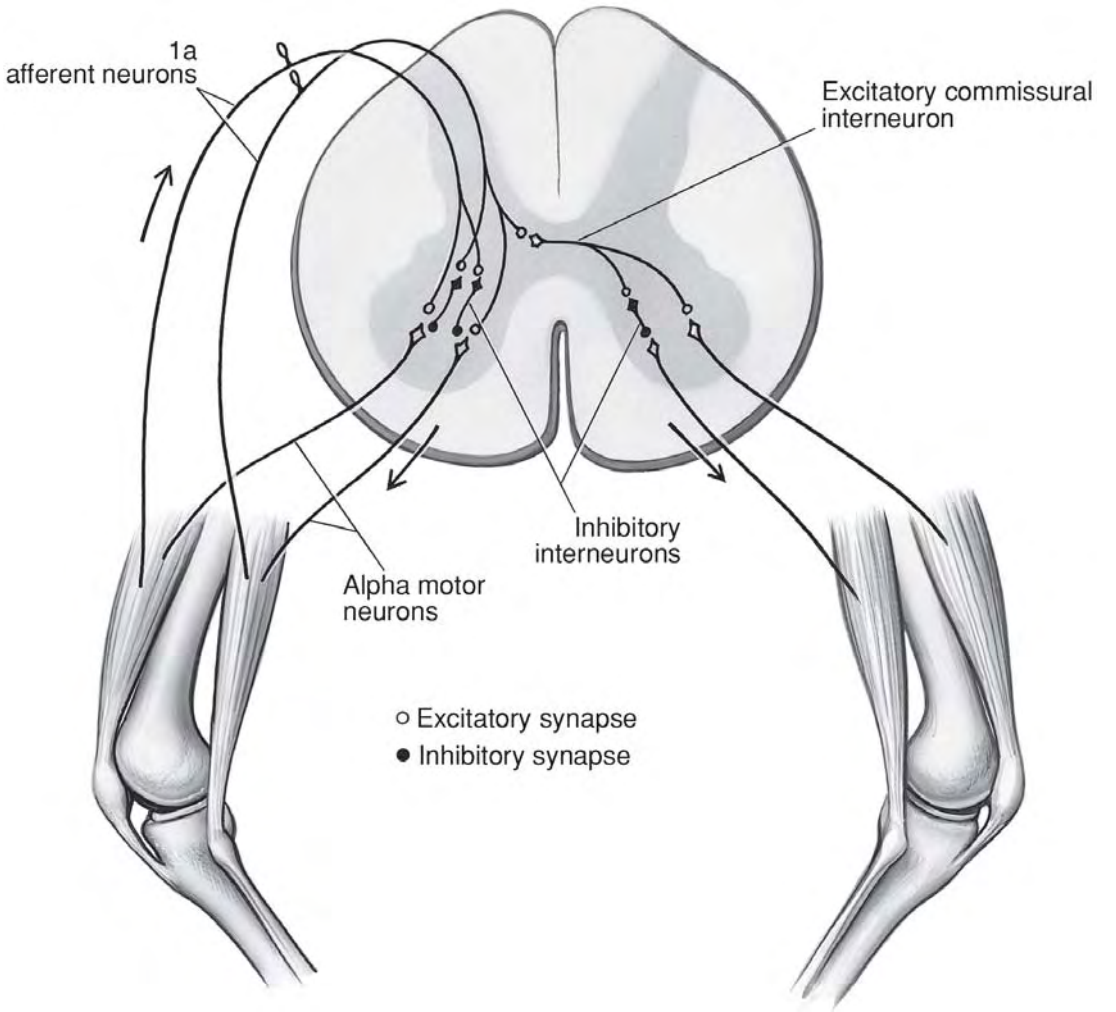


Figure 8.3: Reciprocal innervation of the agonist and antagonist muscles in an ipsilateral reflex (left side) and in a contralateral crossed reflex (right side).

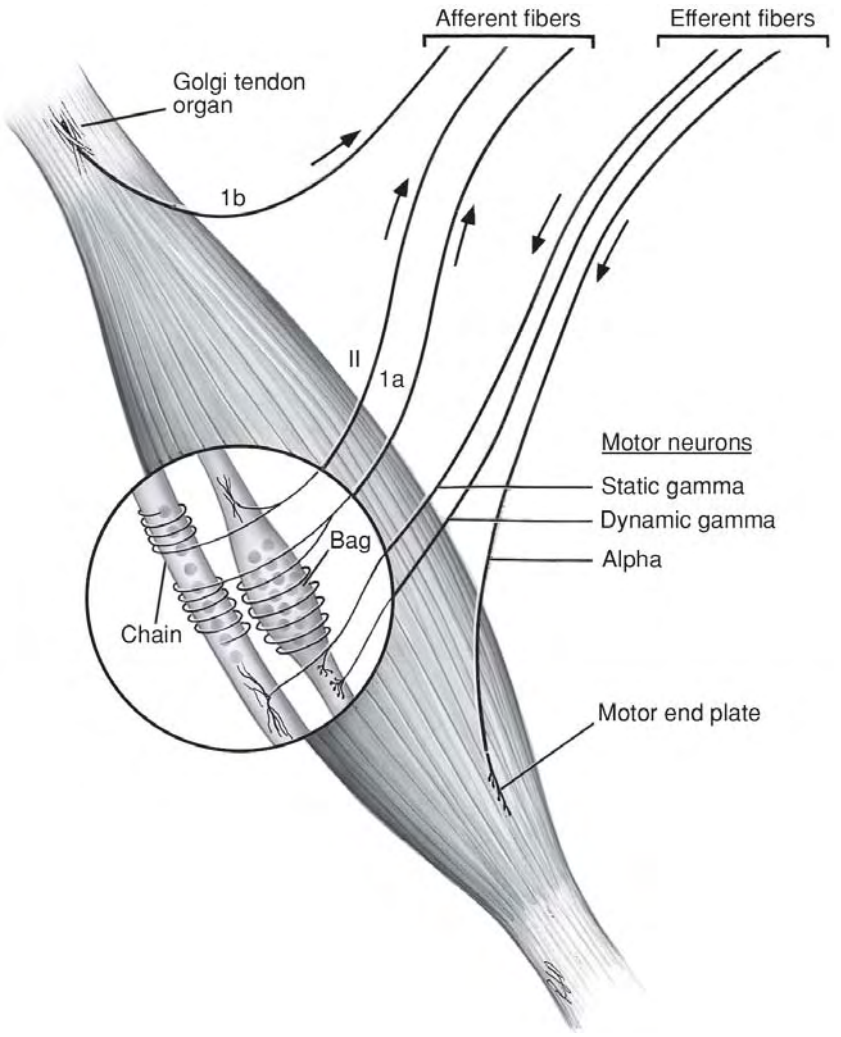


Figure 8.4: Nerve endings in a voluntary muscle and tendon associated with reflexes. The Golgi tendon organ (GTO) consists of afferent terminals intertwined among braided collagenous fibers. The intrafusal muscle fibers in the muscle spindle (enlarged section) are innervated by Ia and group II afferent fibers and by static and dynamic gamma motoneurons. The Ia fiber forms a spiral ending in the bag region of a nuclear bag fiber and in the midregion of a nuclear chain fiber. The group II fiber commences on either side of the primary endings of chain and static bag fibers. Gamma motoneurons terminate in the contractile polar regions of the intrafusal fibers. The static gamma motoneuron terminates as trail endings mainly on the chain fiber and occasionally on a bag fiber. The dynamic gamma motoneuron terminates as plate endings on a bag fiber. The alpha motoneuron terminates as a motor end plate on an extrafusal muscle fiber. The muscle spindle is a stretch-gated receptor (responds to muscle stretch) and the GTO is a tension-gated receptor (responds to muscle tension).

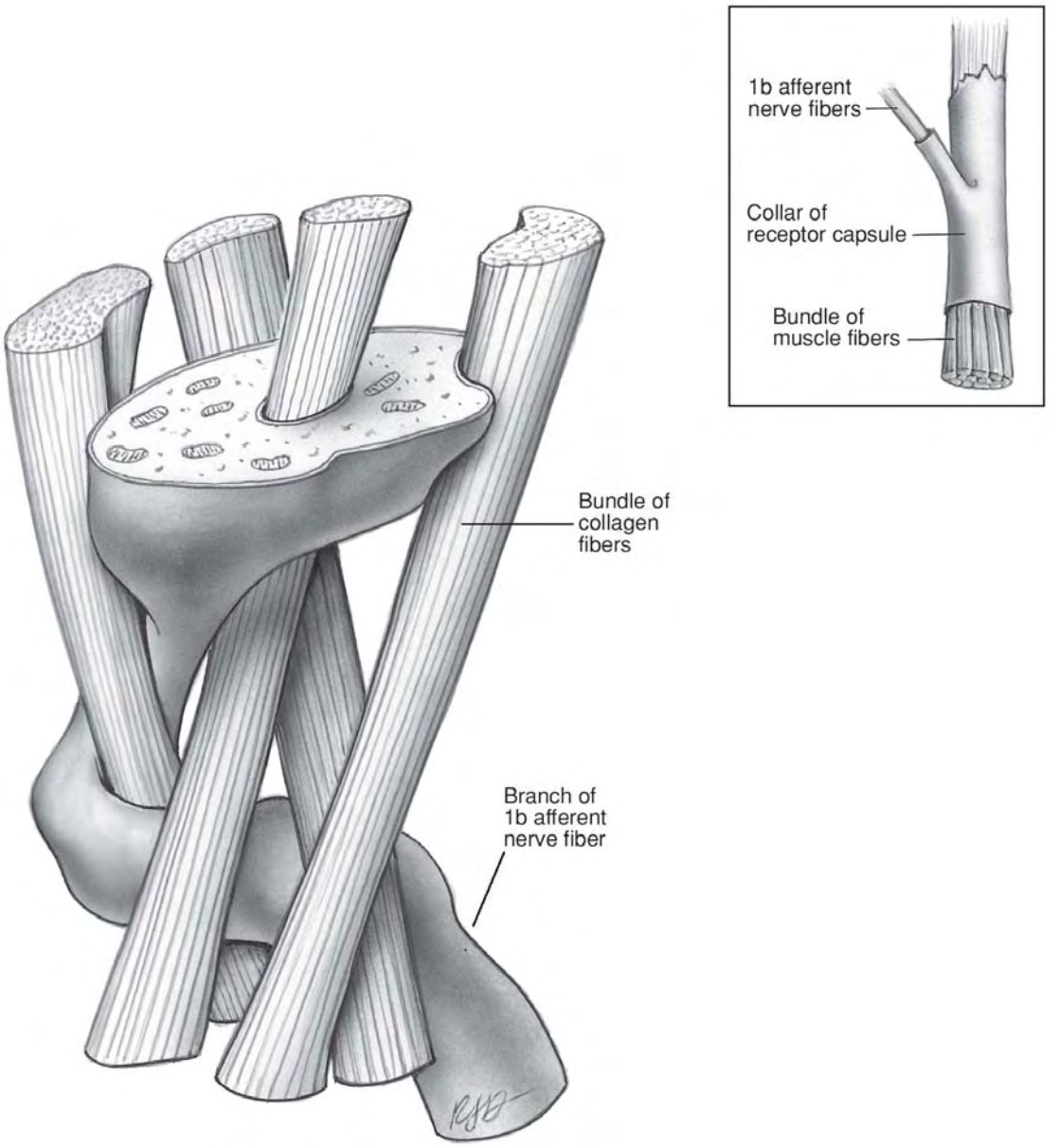


Figure 8.5: Golgi tendon organ (GTO, neurotendinous spindle). The GTO is an encapsulated spindle-shaped sensory receptor at the junction of a bundle of muscle fibers and collagenous fibers of a tendon. It is innervated by 1b afferent nerve fibers. Three-dimensional representation of the relationship of a spiraling nerve ending of a 1b afferent fiber among the collagenous fiber bundles of the tendon. The GTO monitors the degree of tensile forces exerted by the collagenous fiber bundles on the nerve ending when "compressed" by the forces exerted by the contracting muscle fibers. The GTO is similar to one's finger within a braided "Chinese finger wrap"; the more the pull exerted on the wrap (tension from muscle contraction), the straighter the strands of collagenous fibers of the wrap and the greater the squeeze on the finger (GTO).

ascends toward the brainstem; a collateral of each Ia sensory neuron has direct monosynaptic connections with alpha motoneurons within the spinal cord (*see* **Fig. 8.1**). Group Ia fibers from the primary endings of spindles can synapse monosynaptically with alpha motoneurons that innervate the same muscle (called a *homonymous muscle*) or with alpha motoneurons that innervate a synergist. The Ia afferents also can terminate on interneurons, which form inhibitory synapses with alpha motoneurons to an antagonist (called, a *heteronymous muscle*). Group II afferent fibers have direct monosynaptic connections with alpha motoneurons innervating homonymous muscles. Some gamma motoneurons, called *dynamic gamma motoneurons*, are thought to terminate only on bag fibers as plate endings. They are named for their involvement in phasic (motion) reflexes. The other gamma motoneurons, called *static gamma motoneurons*, terminate on bag and chain fibers as trail endings. These neurons are important in tonic (i.e., static or postural) reflexes.

Much of the information from muscle spindles is conveyed via ascending tracts for processing in the brain, especially in the cerebellum and cerebral cortex ("Sensory Areas of the Neocortex"; Chap. 25).

STRETCH (MYOTATIC, DEEP TENDON) REFLEX

Stretch reflexes have an essential role in the maintenance of muscle tone and posture. The simple knee jerk is a *stretch (extensor) reflex* initiated by tapping the tendon of the relaxed quadriceps femoris muscle. Stretch reflexes are *two-neuron* (involving the sequences of an afferent neuron and an efferent alpha motoneuron), *monosynaptic*, *ipsilateral* (reflex restricted to the same side of the body), and *intrasegmental.* A tap on its tendon stretches the quadriceps muscle and many of the neuromuscular spindles. When stretched, the spindles stimulate the group Ia afferent fibers to convey volleys of impulses that (1) monosynaptically excite the alpha motoneurons, which, in turn, stimulate the quadriceps muscle to contract, and (2) through interneurons inhibit the alpha motoneurons innervating the antagonistic hamstring muscles. Thus, the leg extends at the knee joint as the quadriceps suddenly contracts and the hamstrings relax. The brisk knee jerk is initiated by the sudden *synchronous* stretch of many quadriceps muscle spindles. In contrast, the slow continuous contractions maintaining postural muscle tonus are sustained by *asynchronous* stretch and discharge of many spindles over a period of time.

GAMMA REFLEX LOOP

The myotatic reflex acts in the coarse adjustments of muscle tension; the fine adjustments in muscle activity are dependent on the integrity of the gamma reflex loop. Influences from the brain (supraspinal influences) and some peripheral receptors regulate the "set" of the muscle spindles through gamma motoneurons.

The *gamma loop* (*see* **Fig. 8.1**) comprises (1) the efferent gamma motoneuron, (2) the muscle spindle within the voluntary muscle, (3) the group Ia afferent neuron for feedback, (4) the alpha motoneuron, and (5) voluntary muscle fibers. The signals conveyed by the gamma motoneuron alter the sensitivity of the muscle spindle by altering the length of the intrafusal fibers and the tension they exert. As gamma motoneuron activity increases, the set of the muscle spindles is raised to a higher level. This increases the firing rate of the Ia fibers, stimulating the alpha motoneurons. Many of the descending supraspinal influences from the brain do not act directly on alpha motoneurons, but, rather, through the gamma reflex loop.

The *static gamma neurons* are involved preferentially with tonic reflexes (muscle tone). The rigidity associated with increased tonic stretch reflexes (as in Parkinson's disease) might be the result of heightened activity of the static gamma neurons. The *dynamic gamma neurons* are involved with the phasic stretch

reflexes (i.e., contraction of muscles for movement). The spastic signs expressed in upper motoneuron paralysis (Chap. 12) might be the result primarily of increased activity of the dynamic gamma neurons. In effect, the gamma system is critical for continuous fine muscle control. It enables the spindle to maintain a delicate sensibility over a wide range of muscle lengths that are constantly occurring during reflex and voluntary contractions.

GOLGI TENDON ORGAN AND REFLEX LOOP

Golgi tendon organs (neurotendinous spindles) are encapsulated mechanoreceptors located at the junctions of muscles with tendons (*see* **Figs. 8.1 and 8.4**). Within the capsule of the GTO are endings of Ib afferent nerve fibers intertwined among collagenous fibers of the tendon (*see* **Fig. 8.5**). The shortening of the muscle during contraction tightens the braided collagenous fibers, which, by squeezing the nerve endings, generate action potentials. In general, the GTOs in a tendon respond to varying degrees of muscle tension. Specifically, the GTOs within each tendon respond differentially because each GTO is linked through collagenous fibers to a different number of muscle fibers and to different types of motor unit. Thus, different degrees of "squeezing" exerted within a GTO on the Ib ending contribute to the subtlety of the neural influences conveyed from a variety of GTOs to the spinal cord.

This polysynaptic loop comprises (1) the Golgi tendon organ (GTO) in muscle tendons, (2) group Ib afferent fibers, (3) interneurons within the spinal cord, (4) alpha motoneurons, and (5) striated muscle fibers. As the tension within the tendon of a contracting muscle increases, there is an increase in the number of action potentials transmitted via the Ib afferent neurons to an interneuron pool in the spinal cord. These influences tend to inhibit the activity of the alpha motoneurons. The exquisite balance between the excitatory gamma loop and the inhibitory GTO reflex loop is basic to the precise integration of reflex activity. The GTO reflex loop acts to prevent the overcontraction of an agonist muscle and to facilitate the contraction of antagonist muscles through reciprocal inhibition.

FLEXOR REFLEXES

Flexor reflexes are associated with (1) such behavioral responses as protection against a potentially harmful noxious stimuli and (2) such locomotor activities as walking and running. These reflexes are initiated by pain receptors (nociceptors) in the skin (cutaneous), fasciae, and joints, as well as by touch, pressure, and other receptors (*see* **Fig. 8.2**).

Withdrawal, Protective, and Escape Responses

The flexor reflex is fundamentally a withdrawal response from a noxious stimulus. Depending on the seriousness of a potential threat of this type, an individual reacts with protective and even escape responses. Cutaneous receptors in skin and deep receptors in muscles and joints react to intense touch pressure, heat, cold, and tissue trauma, along with the associated pain. These stimuli are conveyed via group II, III and IV (FRA) fibers to interneurons in the CNS. The effect of these inputs is a flexion response through (1) excitation of the alpha motoneurons to the flexor muscles, and (2) inhibition of the alpha motoneurons to the antagonistic extensor muscles. The high intensity of the stimuli results in the spread of the activity via commissural neurons and intersegmental circuits to the contralateral side to evoke crossed extensor reflexes (*see* **Fig. 8.3**) with the synchronous excitation of the extensor lower motoneurons and the inhibition of the flexor lower motoneurons of the contralateral limb. This occurs as, for example, in the act of withdrawing an upper limb following touching a hot object accompanied by shifting the weight to the contralateral lower limb to support the body.

Locomotion

In this activity, the brain contributes by influencing the integrated rhythms of the reflexes of flexion and extension of the upper and lower limbs. The FRAs contribute through multineuronal reflex circuits to inhibit the extensor motoneurons and to simultaneously excite the flexor motoneurons of the lower limb, and to excite the extensor motoneurons and to inhibit the flexor motoneurons of the contralateral limb (*see* **Fig. 8.3**). Through spinal intersegmental circuits, the rhythmic activity of the lower limbs is integrated with the rhythmic activities of the upper limbs, as is characteristic in walking and running.

MUSCLE TONE (TONUS)

Muscle tone is the minimal degree of contraction exhibited by a muscle without conscious effort; it exists even when a muscle is "at rest." When an examiner manipulates an extremity (e.g., flexion and extension) of a relaxed normal individual, the muscle tone is the amount of resistance that is not related to any conscious effort by the patient. Abnormalities of muscle tone are expressed as *hypotonia* (decreased resistance to passive movement) and *hypertonia* (increased resistance to passive movement; Chap. 11).

Hypotonus is not an expression of the isolated muscle so much as an expression of reflex activity upon the muscle. Hypotonia can be produced (1) by severing the ventral roots containing the motor fibers to a muscle or (2) by severing the dorsal roots containing the sensory fibers from a muscle. Lesions of the cerebellum can also result in hypotonia.

Hypertonia is expressed in two forms: spasticity and rigidity. Spasticity combines an increase in resistance to passive manipulation with the "clasp knife" phenomenon along with an increase in deep tendon reflexes (hyperreflexia). The "clasp knife" phenomenon is so named because there is a marked increase in resistance during the initial phases of action, but suddenly the resistance disappears (as when opening the blade of a jack knife). *Rigidity* is expressed as increased tone (hypertonia) in all muscles, although strength and reflexes are not affected. The rigidity can be uniform throughout the range of movement imposed by the examiner (called *plastic* or *lead pipe rigidity*) or it can be interrupted by a series of jerks (called *cog-wheel rigidity* as in Parkinson's disease).

COACTIVATION

Neural influences from the brain via the descending motor pathways to the brainstem and spinal cord circuits elicit the *simultaneous* discharge of both alpha and gamma motoneurons of a particular muscle (Chap. 3). This is known as *coactivation* of these lower motoneurons. Coactivation is essential in the performance of smooth coordinated muscular activity and in sustaining a voluntary contraction. Voluntary activities, ranging from the exquisite movements of a figure skater on ice to the lifting and holding of a heavy object, are largely dependent on the coordinated contractions of muscle fibers.

The following is the sequence of events in coactivation. Stimulation of alpha motoneurons results in the contraction of a muscle with an accompanying shortening of its muscle spindles. This brings about a reduction in the firing rate of the Ia afferents and of the excitatory influences to the alpha motoneurons. This reduction is offset by the stimulation (*coactivation*) of gamma motoneurons innervating the intrafusal fibers of the muscle spindles. By stimulating the intrafusal fibers, these neurons maintain the appropriate firing rate of the Ia afferent fibers, which excite the alpha motoneurons innervating the extrafusal muscle fibers.

The alpha and gamma motoneurons innervating a specific muscle or muscle group are simultaneously stimulated by neurons receiving their influences from segmental and intersegmental circuits and from upper motoneurons originating in the brain.

As compared to alpha motoneurons, gamma motoneurons (1) only innervate intrafusal

muscle fibers, (2) have smaller cell bodies and thinner myelinated fibers, (3) are not excited monosynaptically by afferent fibers from peripheral receptors, (4) are not integrated into the inhibitory Renshaw cell feedback circuit, and (5) tend to discharge spontaneously. The gamma motoneurons are influenced through the descending tracts by the activity of the cerebellum (Chap. 18), reticular system (Chap. 22), and basal ganglia (Chap. 24).

INTEGRATION OF THE SPINAL REFLEXES: ROLE OF INTERNEURONS

Somatic movements are the motor expressions of the integrated activity of the supraspinal pathways from the brain (Chap. 11) and many reflex loops; all are realized through the lower motoneurons. The placement of interneurons within most of these reflex loops adds to the complexity and versatility of the motor control.

The descending motor supraspinal pathways from the brain influence either (1) indirectly by synapsing with interneurons integrated into spinal neural circuits or (2) directly by synapsing with the lower motoneurons. The alpha motoneurons are stimulated primarily through indirect supraspinal connections. Some fibers of the corticospinal tract, lateral vestibulospinal tract, reticulospinal tracts, and raphe–spinal tract make monosynaptic connections with the alpha motor neurons. These alpha motoneurons contribute to the intrinsic spinal circuitry through collateral branches that excite interneurons called *Renshaw cells* (*see* **Fig. 3.11**). In turn, the excited glycinergic Renshaw cells are intercalated in a negative feedback circuit that directly inhibits the same alpha motoneuron. This tends to turn off the firing activity of the alpha motoneuron so that it will be ready to respond to firing again in response to excitatory stimulation. *Intersegmental interneurons* convey influences from one spinal segment via axons to one or more other spinal segments on the same side of the spinal cord. These neurons are connected with commissural interneurons (*see* next paragraph) and together they act in such integrated rhythmic movements of the upper and lower extremities as walking and running. However, interneuronal circuits are crucial in all movements. For example, in a smooth flexion movement, the flexor (agonist) muscle group contracts while the extensor (antagonist) muscle group relaxes for this type of action; reciprocal inhibition and feedback inhibition are required. In *reciprocal inhibition*, by means of interneurons the lower motoneurons innervating the agonist muscles are excited while those innervating the antagonist muscles are inhibited. In *feedback inhibition*, the interneurons selectively inhibit the lower motoneurons so that each agonist group contributes by contracting to the proper degree to perform the movement.

Commissural interneurons relay influences from one side across the midline to the gray matter of the contralateral side. These are important in *crossed extensor reflexes* (*see* **Fig. 8.3**). The extremity opposite to that in which the FRA fibers are stimulated responds in the reverse fashion; that is, the extensor muscles contract and the flexor muscles relax. This crossed (extensor) reflex utilizes the commissural neurons to relay neural information to the opposite side. A painful stimulus to the foot (stepping on a tack) evokes a reflex flexor withdrawal of the ipsilateral extremity and especially an enhancement of extensor musculature contractions of the contralateral extremity to enable the contralateral extended limb to support the body while the flexed ipsilateral extremity is off the ground. The interplay of these crossed reflexes is utilized in the alternate rhythms of both upper and lower extremities during running and walking.

The afferent neurons innervating the sensory receptors are integrated into the spinal reflexes for feedback purposes. In addition to their role as monitors of new and naive information, the receptors sense the effects of motor activity and feed this information back to the CNS. Through this input, the circuitry within the CNS is continuously informed of its effects on muscular activity. In this role, these neurons are known as feedback (reafferent or re-entry) neurons.

The receptors at work in this feedback schema are known as direct receptors and indirect receptors. Direct receptors (the muscle spindles) are directly innervated by gamma motoneurons from the CNS and, thus, are integrated into direct feedback circuits. *Indirect receptors*, such as the GTO, joint, and cutaneous receptors, do not have a direct efferent innervation from the CNS and, thus, are integrated into so-called indirect feedback circuits.

SUGGESTED READINGS

Brooks VB. *The Neural Basis of Motor Control.* New York: Oxford University Press; 1986.

Desmedt J. *Motor Control Mechanisms in Health and Disease.* New York: Raven Press; 1983.

Freund HJ. Motor unit and muscle activity in voluntary motor control. *Physiol. Rev.* 1983;63: 387–436.

Freund HJ. Functional organization of the human supplementary motor area and dorsolateral premotor cortex. *Adv. Neurol.* 1996;70:263–269.

Freund HJ. Mechanisms of voluntary movements. *Parkinsonism Relat. Disord.* 2002;9:55–59.

Gandevia SC, Refshauge KM, Collins DF. Proprioception: peripheral inputs and perceptual interactions. *Adv. Exp. Med. Biol.* 2002;508:61–68.

Hasan Z. Role of proprioceptors in neural control. *Curr. Opin. Neurobiol.* 1992;2:824–829.

Jewett DL, Rayner MD. *Basic Concepts of Neuronal Function: A Multilevel Self-Teaching Textbook.* Boston: Little, Brown; 1984.

Matthews PB. What are the afferents of origin of the human stretch reflex, and is it a purely spinal reaction? *Prog. Brain Res.* 1986;64:55–66.

Matthews PB. Proprioceptors and their contribution to somatosensory mapping: complex messages require complex processing. *Can. J. Physiol. Pharmacol.* 1988;66:430–438.

Matthews PB. The human stretch reflex and the motor cortex. *Trends. Neurosci.* 1991;14:87–91.

Matthews PB. Spindle and motoneuronal contributions to the phase advance of the human stretch reflex and the reduction of tremor. *J. Physiol.* 1997;498(Pt. 1):249–275.

Phillips CG. Motor apparatus of the baboon's hand. *Proc. R. Soc. Lond. B. Biol. Sci.* 1969;173: 141–174.

Phillips CG. Central control of movement. How can one discover the relative functional roles of pyramidal inputs to alpha as compared to gamma motoneurons? *Neurosci. Res. Program Bull.* 1971;9:135–139.

Phillips CG. Proceedings: Hughlings Jackson Lecture. Cortical localization and "sensori motor processes" at the "middle level" in primates. *Proc. R. Soc. Med.* 1973;66:987–1002.

Sherrington CS. *The Integrative Action of the Nervous System.* Originally published: New York: Scribner's, 1906. London: Routledge/Thoemmes; 2002.

9
Pain and Temperature

Features of Sensory Systems
Receptors
Afferent (First-Order) Neurons
Pathways From the Body, Limbs, and Back of Head
Major Classes of Functionally Defined Neurons and the Spinothalamic Tracts
Wall's Concept of Pain in Target Motor Responses
Pathways From the Anterior Head
Temperature (Thermal) Sense
Perception of Pain
The Gate Control Theory of Pain Modulation
Descending Control Mechanisms of Pain Modulation
Endogenous Pain Control
Referred (Transferred) Pain
Stimulus-Induced and Stressed-Induced Analgesia
Central Pain Syndrome (Thalamic Syndrome)
Phantom Limb Sensation
Somatotopic Organization of the Lateral Spinothalamic Tract

We perceive the external world and become alert, create body image, and regulate our movements through sensory systems. The term *somatosensory system* refers to the sensory receptors that respond to a particular physical property (e.g., temperature), together with tracts and nuclei that transmit information about four major general somatic modalities—the sensations of *pain* (signaling tissue damage or chemical irritation), *temperature* (warmth or cold), *touch*, (for recognition of size, shape, and texture), and *proprioception* (sense of static position and movements of the limbs, body, and head) (*see also* Chap. 10). Somatosensory receptors are located in the skin, muscles, joints, and viscera, a distribution that makes this system the largest and most varied of the sensory systems. Although primarily sensory, this system also is of importance in the control of coordinated movements by providing appropriate feedback to the *somatic motor system* about joint position, muscle tension, velocity of muscular contractions, and contact of the body with external surfaces (Chaps. 8 and 11). Sensations occur when stimuli interact with receptors (sensors). Sensory information then is transmitted cephalically as patterns of action potentials by individual neurons and by assemblies of neurons acting in consort. All sensory systems, regardless of modality, transmit information pertaining to the intensity, duration, and location of the stimuli that activate them.

There are four classes of somatic sensory receptor, each of which is sensitive to one form of physical energy. These are sensors for a variety of mechanical, thermal, chemical and electromagnetic events. (Photoreceptors in the retina are the only electromagnetic energy

detectors in humans.) The specificity of each modality is maintained within the nervous system by being segregated into discrete anatomical pathways and processing centers. As a schema, every general sensory system consists of a core sequence of primary afferent fibers, relay nuclei located in the spinal cord, brainstem, and thalamus, together with interconnections and culminating at the cerebral cortex. Each processing nucleus not only consolidates inputs from adjacent receptors but also integrates signals from inhibitory neurons and descending projections to transform and enhance the sensory information (*see* **Fig. 3.13**).

The nervous system responds to stimuli from a variety of environmental energies that are sensed by receptors associated with each modality. The recipient information is transmitted by neurons with their cell bodies located in the dorsal root ganglia or its equivalent ganglia in the cranial nerves to neurons within the central nervous system (CNS). The receptor for each modality has a singular morphological and functional specialization that monitors a specific type of environmental stimulus.

Pain sensations are mediated by nociceptors (free nerve endings) that are stimulated by tissue-damaging impacts such as pinching or injury and chemical substances released from tissue cells physically damaged or injured from extreme heat or cold resulting from burns and frostbite (Chap. 9). Temperature is sensed by naked nerve endings of unmyelinated or lightly myelinated nerve fibers. These endings sense what is then processed into the everyday perceptions of cool, cold, warmth, and hot sensations. Discriminative touch is a mental response to signals from encapsulated receptors sensitive to physical distortions, indentations, and movements across the skin (Chap. 10). Proprioception refers to stretch or contractions of muscles and joint movements involving the head, trunk, and limbs (Chap. 10). Spatial resolution, mediated by mechanoreceptors, is most accurate on the fingertips and lips, where these sensors are most abundant. Proprioceptors utilize pressure and motion to sense the shape and surface texture of objects handled.

FEATURES OF SENSORY SYSTEMS

The term *sensory* is used to include all afferent input from the peripheral nerves, whether consciously perceived or not. *Sensations* are conscious perceptions and experiences associated with stimuli arising directly from the stimulation of receptors of the sense organs. The *sensory systems* are involved in (1) the awareness of sensations, (2) the unconscious inputs that underlie the control of movements and many bodily functions, and (3) neural activities associated with arousal. The sensory systems have evolved to provide information from both the internal and external environments of the organism. *Receptors* are the monitors sensing the environment. They are involved with *transduction*, which is the conversion of stimulus energy into neural activity. The quality of each stimulus results in a form of sensation called a *modality,* such as pain, thermal sense, touch, or vision. Each modality has submodalities (e.g., vision—perceptions of color, form, depth, and motion). The three receptor types and some associated modalities are (1) *mechanoreceptors* such as temperature (thermal), noxious (pain or nociceptors), auditory (sound) and touch receptors. (2) *chemoreceptors* (taste and smell) and (3) *photoreceptors* (light). Transduction in a mechanoreceptor is brought about by the direct mechanical interaction of a stimulus with the channels on a receptor membrane. In an unstimulated membrane, only a few channels are open. When the receptor membrane is deformed by a stimulus, more channels open and Na^+ and K^+ shift to produce depolarization, called the receptor potential. Transduction in a chemoreceptor results from the interaction of a chemical with a receptor linked to a second-messenger system to mediate channel openings. This is the means utilized by olfactory receptors and certain gustatory receptors. The transduction in a photoreceptor is associated with absorption of light by the membranous disks of the rods and cones of the retina. The resulting change in receptor membrane permeability involves a second-messenger system.

Four distinct elementary general somatic modalities are recognized: (1) *pain* elicited by noxious stimuli in damaged tissue (Chap. 9), (2) *thermal sensations* elicited by warm and cool stimuli, (3) touch elicited by mechanical stimuli applied to the body (Chap. 10), and (4) *proprioceptive sensations* elicited by the mechanical displacement of muscles and joints (Chap. 10).

Two major *general sensory systems* are associated with sensory input from the spinal nerves from the body. Equivalent systems are associated with similar input from the head (e.g., from the trigeminal nerve). They are (1) the anterolateral system of pathways for pain and temperature and somewhat for touch and (2) the dorsal column–medial lemniscal system of pathways for touch and proprioception (Chap. 10). Each of the systems is organized (1) with most of the sensory submodalities conveyed by functionally separate pathways, (2) hierarchically with successive serial processing centers (called relay nuclei) terminating at the cerebral cortex, and (3) for parallel processing at each level (Chap. 3). These two systems and their pathways converge on distinct and separate populations of neurons within the ventral posterior nucleus of the thalamus. From the thalamus, neural information is projected to the sensory areas of the cerebral cortex, where the various submodalities are integrated into the experience of perception. It is at these higher centers that the several aspects of sensations are finely honed, including (1) quality (e.g., pain), (2) intensity, (3) location on body, (4) duration, and (5) affect (e.g., range from pleasant to unpleasant). It is these attributes that make a perception more than a sensation.

The pathways of the general sensory systems usually consist of a sequence of first-order, second-order, and third-order neurons. The *first-order neurons* are those peripheral sensory neurons with cell bodies in spinal dorsal root ganglia, or cranial nerve ganglia, and axons that terminate in the spinal cord or brainstem. S*econd-order neurons* are those with cell bodies in the nuclei of the spinal cord and/or brainstem with axons that ascend to terminate in the thalamus. An assembly of axons of second-order neurons is called a tract (fasciculus or pathway) in the white matter of the spinal cord and could be called a lemniscus (ribbon) in the brainstem. *Third-order neurons* are those with cell bodies in the thalamus and axons that terminate in the somatosensory cortex (areas 3, 1, and 2) of the parietal lobe.

The centers and nerve fibers involved with the processing and transmission of signals resulting in the conscious appreciation of pain and temperature are in such close proximity that their pathways are collectively called the *pain and temperature pathways*.

RECEPTORS

Receptors have been variously classified. *Exteroceptors*, located near the body surface, are generally stimulated by external environmental energies. They are sensed as touch, light touch, pressure touch, pain (noxious stimuli), temperature, odor, sound, taste, or light. *Proprioceptors* are located within deep structures of the head, body wall, and extremities. Proprioception includes such modalities as position sense, vibratory sense, balance, and sense of movement. *Interoceptors* monitor the viscera and project information sensed as cramps, pain, and fullness and are utilized in visceral reflexes (e.g., carotid sinus reflex). *Mechanoreceptors* respond to mechanical stimuli (touch, hearing). *Chemoreceptors* respond to chemical stimuli (taste, smell). C*hemesthesis* is now recognized as a common chemical sense comprising irritant-detecting receptors, resembling pain receptors (nociceptors), that are sensitive to chemicals applied to the skin, mucosal membranes of the oral cavity, nasal cavities, respiratory tract, and genital orifices. The free nerve endings that respond to chemicals including irritants do not constitute a separate, independent sense, but, rather, are part of the general somatic nervous system. The chemosensitive fibers appear to be a subset of pain and temperature fibers. *Thermore-*

ceptors (temperature receptors) respond to various degrees of warmth and cold.

Peripheral Pain Mechanisms

Receptors of "painful" stimuli are collectively referred to as *nociceptors*. They are free (naked) nerve endings that respond to direct stimulation and to chemical products associated with local injury (noxious stimuli) (*see* **Figs. 10.1 and 10.2**). Three types of free nerve ending receptor are associated with two types of afferent fiber. On the basis of functional criteria, they are (1) mechanosensitive nociceptors with A-delta fibers, (2) mechanothermal nociceptors with A-delta fibers, and (3) polymodal nociceptors (respond to thermal, mechanical, thermal, and chemical stimuli) with C fibers (*see* **Fig. 9.1**). Following trauma, chemical mediators are released locally from the damaged tissues that can sensitize and, at times, activate the nociceptors of the A-delta and C fibers. Two such agents are the eicosanoid prostaglandins that are sensitizers derived from injured cells and the peptide bradykinin that is an activator derived from plasma kininogens. The activation of nociceptors results in the release from C fiber terminals of the peptide substance P that, in turn, causes mast cells to release histamine, which excites nociceptors. The edema associated with an injury results from the actions of substance P, which produces plasma extravasations, and of calcitonin gene-released peptide that results in the dilation of blood vessels. In addition, the edema causes

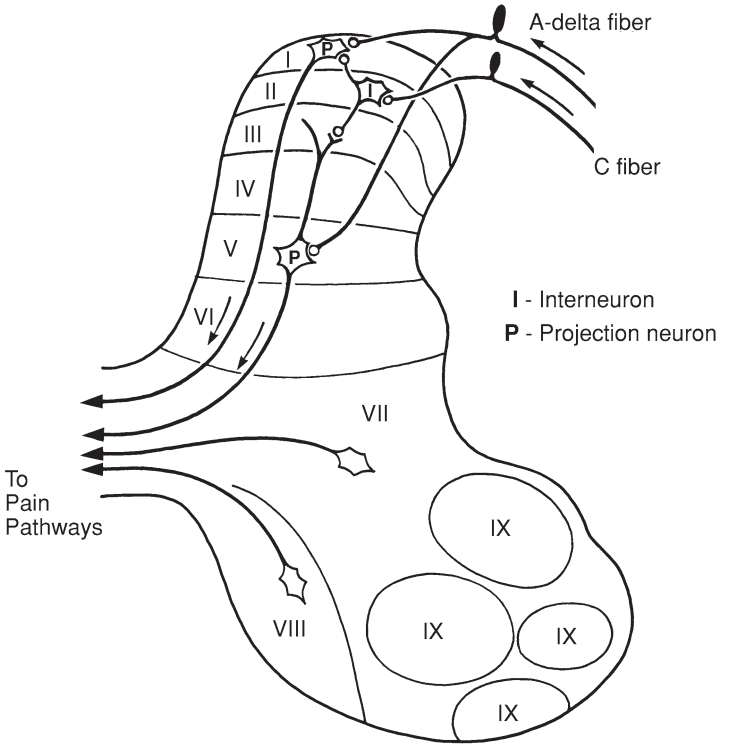


Figure 9.1: Spinal cord terminations of dorsal root fibers that mediate pain. The A-delta fibers (pain, temperature, and touch) terminate in laminae I and V, where they synapse with projection neurons (P) whose axons ascend in the pain pathways illustrated in Fig. 9.2. The C fibers (pain and temperature) terminate in lamina II. Interneurons (I) in lamina II have axons that synapse with projection neurons in laminae I and V. (Refer to **Table 7.4**.)

release of more bradykinin. Other chemical mediators include (1) serotonin (5HT) derived from platelets, (2) potassium ions derived from damaged tissue cells acting as activators of nociceptors, and (3) substance P released from the afferent nerve terminals acting as a sensitizer of nociceptors. The effectiveness of aspirin and other anti-inflammatory analgesics in the control of pain occurs because they inhibit an enzyme involved in the synthesis of prostaglandins. The subjective perception elicited by a brief, intense stimulus is of a sharp, short-duration pain (first pain) followed by a dull, prolonged pain (second pain). First, pain is transmitted by the A-delta fibers that convey information from the thermal and mechanical receptors. Second, pain is transmitted by C fibers activated by polymodal receptors. The viscera contain *silent receptors.* Usually, these receptors are activated by noxious stimuli. However, their stimulation (firing threshold) is markedly reduced by inflammation and a variety of chemicals that produce a syndrome called hyperalgesia (excessive response to a minimal stimulus that is often perceived spontaneously).

To distinguish between nociception and pain is basic to an understanding of sensory systems. *Nociception* implies the reception by nociceptors of stimuli that form signals to provide information to the CNS of tissue damage eliciting a noxious stimulus. Pain is the perception of an unpleasant sensation. *Perceptions*, such as pain, are abstractions of the sensory input by the CNS. Pain is said to be a subjective perception with a psychological dimension. A noxious stimulus that triggers a nociceptor to respond is not necessarily perceived as pain.

Neurologists usually test for cutaneous pain simply by pricking the skin with a sterile, disposable, hypodermic needle. Thermal sensibility is evaluated by applying a tube containing ice (40°F) and another containing warm water (110°F) to a body part. Temperature differences of 5–10°F are normally detected subjectively.

The thermal receptors sensing heat and cold are located in free nerve endings. Small shifts in the skin temperature, of about 0.2°F, are sufficient to alter the firing rate of the endings. In essence, thermoreceptors are not objective sensors of actual skin temperature; rather, their role is to signal information resulting in adjustments to the environment. A perception is especially vigorous when the change is rapid. For example, the perception of hot occurs when a "cold" hand is placed in lukewarm water. Also, a momentary distorted feeling of coolness is perceived when a foot is placed in a bathtub with hot water.

AFFERENT (FIRST-ORDER) NEURONS

Pain and temperature inputs are conveyed via two types of first-order afferent neuron whose cell bodies are in dorsal root ganglia, or the trigeminal ganglion: (1) faster-conducting, lightly myelinated A-delta fibers and (2) slow-conducting, unmyelinated C fibers (*see* **Fig. 9.1**); maximum velocities are 30 and 2 m/s, respectively (*see* **Table 7.4**). The A-delta afferents have low-threshold receptors and conduct signals perceived as sharp localized pain. The C fiber afferents have high threshold receptors and are involved in diffuse persistent pain that might possess aching, burning, or itching qualities. Diffuse pain, presumably the result of released chemicals, often is preceded by sharp stabbing pain.

Neurons excited exclusively by nociceptors are called *nociceptive-specific neurons*. Other first-order neurons involved with the pain pathway conveying input from low-threshold mechanoreceptors are called *wide dynamic range neurons*. Both the A-delta and C fibers release the excitatory transmitter glutamate and various neuropeptides, especially substance P.

The A-delta afferents, with low-threshold receptors, conduct impulses perceived as sharp, pricking sensations that are accurately localized and categorized as *fast* or *initial pain*.

The C afferents, with high-threshold receptors, sense pain as a burning sensation with a slower onset and as a more persistent and less distinctly localized modality known as *slow* or *delayed pain*. Both fast pain and slow pain are

essentially somatic sensations from superficial receptors in the body.

In addition, *deep* or *visceral pain*, subjectively characterized as aches with at times a burning quality, results from stimulation of deep somatic and visceral receptors. This form of pain is associated with inputs conveyed by A-delta and C fibers in both somatic and visceral nerves.

Stimulation of *mechanoreceptor nociceptors* (e.g., from a knife cut or pin prick) and *thermal nociceptors* in free nerve endings evokes a neural code that is conveyed via A-delta fibers and perceived as sharp and pricking pain (or temperature). Stimulation of thermal and *polymodal nociceptors* (mechanical, heat, and chemical noxious stimuli) in free nerve endings evokes codes that are conveyed by C fibers and perceived as slow, burning pain (or temperature). Thermal nociceptors respond selectively to heat and cold. In humans, heat receptors respond selectively when the temperature exceeds the heat pain threshold of 113°F. Cold receptors respond to noxious cold stimuli.

Pain in Dermatomes

A dermatome is a sensory segment of skin innervated by fibers from one dorsal root (*see* **Fig. 7.3**). Dermatomes from successive spinal segments overlap. Hence, the interruption of one complete dorsal root could result in only the diminution (not loss) in sensation in part of the dermatome. However, the irritation of a dorsal root can produce pain in one or more dermatomes. In *herpes zoster* (*shingles*), there is an intense and persistent pain in one or more dermatomes. This pain is a consequence of the activation of pain fibers by vericella zoster virus, which primarily affects one or more dorsal root ganglia or the trigeminal ganglion. Mechanical compression (e.g., following a slipped disk) of a dorsal root can irritate the dorsal root and produce pain over a dermatome.

PATHWAYS FROM THE BODY, LIMBS, AND BACK OF HEAD

Pain and temperature pathways from the body, limbs and back of the head, posterior to the coronal plane through the ears (*see* **Fig. 9.2**), are components of the *anterolateral pathway* (located in the white matter of the anterolateral quadrant of the spinal cord). The tracts are the (1) *(lateral) spinothalamic tract,* terminating in the thalamus, (2) *spinomesencephalic tract,* terminating in the periaqueductal gray (PAG) of the midbrain, and (3) *spinoreticular tract,* terminating in the brainstem reticular formation. The *anterior spinothalamic tract* conveying light touch is included in the anterolateral pathway (*see* **Fig. 10.3**). Additional fibers conveying nociception are incorporated in the spinocervicothalamic pathway located in the dorsal columns of the lemniscal system (Chap. 10).

The A-delta and C fibers enter the spinal cord as the lateral bundle of the dorsal root. They bifurcate into branches that ascend and descend one or two spinal levels in the *posterolateral fasciculus* (*tract of Lissauer; see* **Fig. 7.6**), from where they enter and terminate in the dorsal horn (*see* **Fig. 9.2**). The A-delta fibers have excitatory synapses with projection neurons. The C fibers synapse with interneurons interacting with (1) projection neurons whose axons ascend to higher centers in the brain and (2) inhibitory interneurons that modulate the flow of nociceptive information to higher centers. The A-delta fibers synapse with neurons in laminae I, II, and V; C fibers synapse with neurons in laminae I and II. Branches of each fiber terminate in several spinal levels. According to the gate control theory (*see* **Fig. 9.3**), processing of these inputs occurs within the dorsal horn by interactions involving nociceptive-specific neurons, wide dynamic range neurons, interneurons, and projection neurons. Descending control mechanisms also are important in pain modulation (*see* **Fig. 9.4**).

Cells in several laminae contribute differentially to separate components of the spinothalamic tract. About half of the fibers arise from lamina I, and the rest arise equally from laminae IV–V, and VII–VIII. Roughly 90% of the second-order fibers decussate; the remainder ascends ipsilaterally.

The pain and temperature pathways terminate in several thalamic nuclei including but

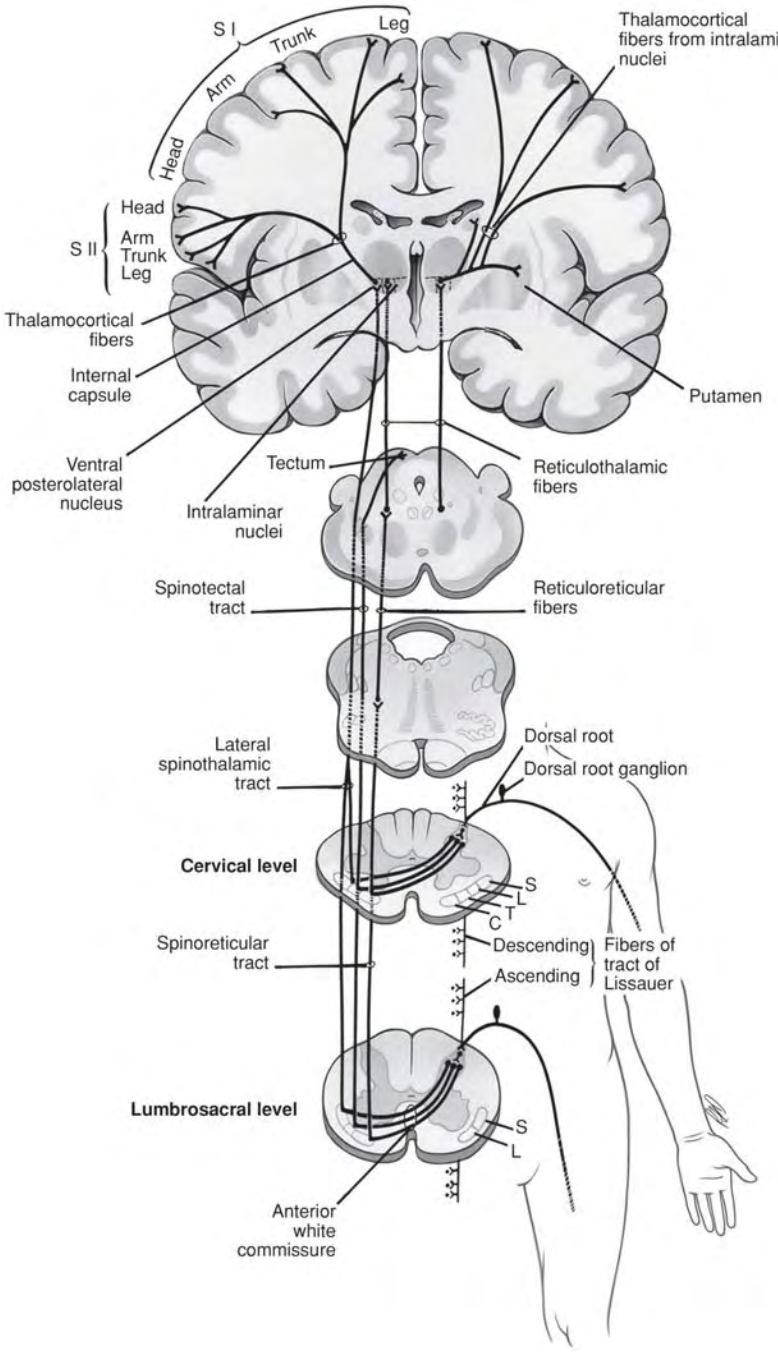


Figure 9.2: The pain and temperature pathways originating in the spinal cord: the lateral spinothalamic tract, spinomesencephalic (spinotectal), and spinoreticulothalamic fibers. Note that the ventral posterolateral (VPL) thalamic nucleus projects to the body regions of both SI and SII of somatosensory cortex and that the intralaminar thalamic nuclei project diffusely and widely to the cerebral cortex. The lamination of the lateral spinothalamic tract is shown on the right side of the cross-sections of the spinal cord (C, cervical; T, thoracic; L, lumbar; S, sacral levels).

not limited to the ventral posterolateral nucleus (VPL), posterior nucleus (PTh), and intralaminar nuclei (Chap. 23). VPL and the ventral posteromedial nucleus (VPM), which receives somatosensory information from the head, are called the ventrobasal complex (VB). In terms of the nature of the nociceptive inputs, there are two significant differences between these thalamic nuclei: (1) The intralaminar nuclei, activated via the spinoreticulothalamic pathway, receive input from neurons of spinal laminae VI, VII, and VIII conveying information from large complex nociceptive fields; (2) VB and PTh, part of the ventral group of thalamic nuclei, receive input from laminae I and V via the spinothalamic pathway, which conveys information primarily from nociceptive-specific and wide dynamic range neurons.

The *(lateral) spinothalamic tract* originates from projection neurons of laminae I, V, VI, and VII. After the axons of its s*econd-order neurons* decussate in the *anterior white commissure* (anterior to central canal), they ascend in the anterolateral pathway and terminate primarily in VPL and PTh thalamic nuclei (*see* **Fig. 9.2**). Some collateral branches terminate in the brainstem reticular formation. This tract conveys information perceived with an overlay of the discriminative aspects associated with various subtleties associated with the sensation

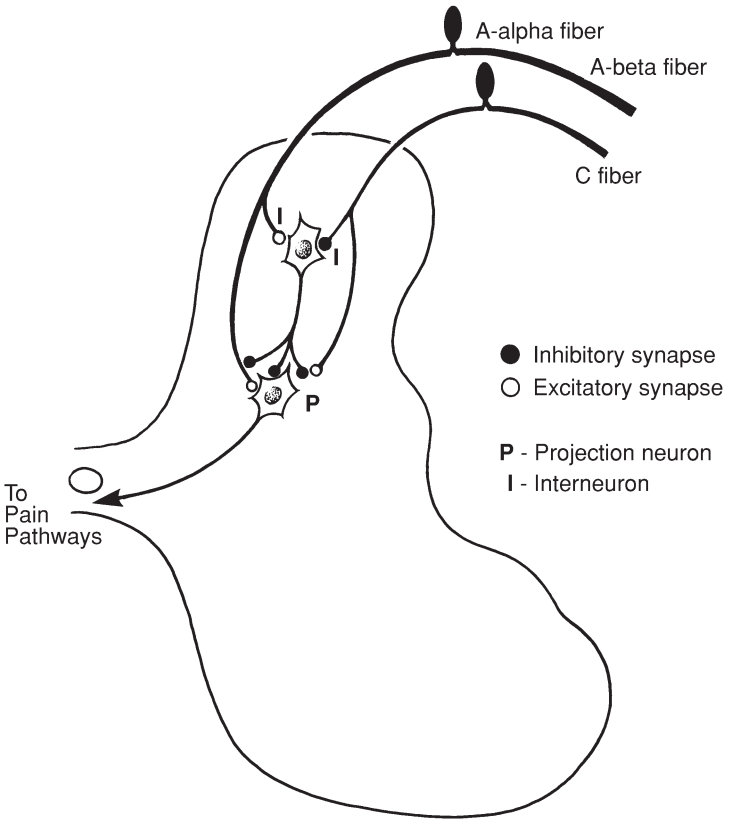


Figure 9.3: Gate control model for pain modulation. The model postulates the interaction of (1) the C pain fibers that have inhibitory synapses with an interneuron and excitatory synapses with a projection pain neuron, (2) the myelinated A-alpha and A-beta non-nociceptive fibers that have excitatory synapses with both the interneuron and the projection pain neuron, and (3) the interneurons that have inhibitory synapses with the projection pain neuron. See text for further explanation.

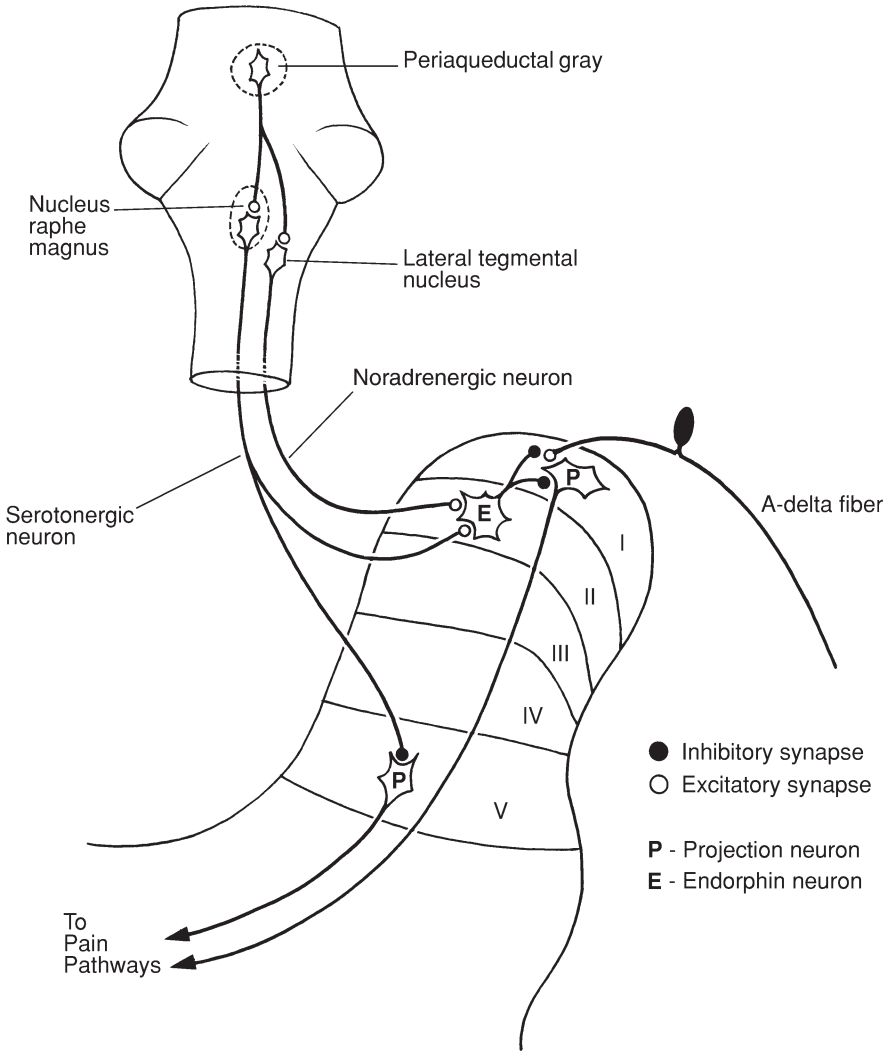


Figure 9.4: Pain control and modulation. Pain can be modulated by the release of opioid peptides. Neurons of the periaqueductal gray in the midbrain have excitatory synaptic connections with serotonergic neurons in nucleus raphe magnus and with noradrenergic neurons in the lower brainstem reticular formation. The serotonergic neurons (1) have inhibitory synapses with nociceptive projection neurons and (2) excitatory synapses with endorphin-containing interneurons (E), which have inhibitory synapses with the nociceptive projection neurons (P). The noradrenergic (norepinephrine) neurons also have excitatory synapses with the endorphin-containing interneurons. These activities modulate the excitatory synaptic influences of the glutamate and substance P transmitters of the A-delta fibers with the nociceptive projection neurons.

of sharp pain and, in addition, with thermal sense (temperature).

At successively higher levels of the spinal cord, new fibers join the tract on its medial aspect; this produces a laminated *somatotopically organized* tract; that is, each body segment (or dermatome) is represented in a portion of the tract (*see* **Fig. 7.6**). As a conse-

quence, in the upper spinal cord, pain and temperature fibers from the sacral region are located posterolaterally and those from the sacral region are located anteromedially. The VPL thalamic nucleus is also somatotopically organized with the sacral and lumbar (lower body) levels located laterally and the thoracic and cervical levels medially. This tract is also called the *lateral pain system* or *neospinothalamic tract* (meaning new phylogenetically).

Axons of the *third-order pain and temperature neurons* located in the thalamus ascend through the posterior limb of the internal capsule and corona radiata and terminate in the parietal lobe of the cerebral cortex (Chap. 25). Fibers from VPL terminate in lamina IV of the *primary somatosensory cortex* (SI; areas 3, 1, and 2 of the postcentral gyrus), whereas fibers from PTh terminate in lamina IV of the secondary somatosensory cortex (SII; areas 3, 1, and 2 near the lateral fissure; Chap. 25). The thalamus might be associated with the perception of pain, whereas the parietal lobe and other cortical areas are involved in the appreciation and the localization of pain and of the integration of stimuli from the pain pathways with the other sensory modalities.

The *spinomesencephalic tract* is composed of the fibers of projection neurons in laminae I and V that decussate in the anterior white commissure and ascend in the anterolateral pathway. It terminates in the periaqueductal gray (PAG) of the midbrain (*see* **Fig. 9.4**) and is involved in the modulation of pain and in the functioning of the reticular system (Chap. 22).

The *spinoreticular tract* is integrated into the *spinoreticulothalamic* pathway terminating in the intralaminar thalamic nuclei (Chap. 21). The spinoreticular fibers originate from neurons in laminae VII and VIII, which receive inputs from large, complex, receptive fields in the periphery. The spinoreticular tract consists of crossed and a few uncrossed fibers that, along with collateral fibers from the spinothalamic tract, terminate in the multineuronal, multisynaptic complex known as the brainstem reticular formation (Chaps. 13 and 22). Reticulothalamic fibers terminate in the intralaminar nuclei of the thalamus, in the hypothalamus, and in limbic structures. From the spinal cord, there are direct projections to the hypothalamus. This slowly conducting multisynaptic pathway conveys diffuse poorly localized pain from both somatic and visceral sources. The intralaminar nuclei project to widespread areas of the cerebral cortex, including the frontal lobes. The influences exerted by this pathway are integrated into autonomic and reflex responses to pain and to affective–motivational responses. As a consequence, this pathway is also called the *paramedian pain pathway* or the *paleospinothalamic pathway* (old phylogenetic pathway) or *medial pain system*.

The neospinothalamic pathway, via the VPL nucleus, projects to the primary and secondary somatic sensory areas of the cerebral cortex. These are essential for spatial and temporal discrimination of painful sensations. In contrast, the paleospinothalamic pathway mediates the autonomic and reflexive responses associated with pain and, in addition, the emotional and affective responses.

The roles of the cerebral cortex and the thalamus in the perception of pain are complex. Several clinical observations following certain surgical procedures are relevant to an understanding of the perception of pain. Surgical intervention in various locations, both of the peripheral and central nervous systems, has not proven to be effective in permanently relieving pain. Surgery can abolish the perception of pain temporarily, but it subsequently can return with new manifestations that are unpleasant and frequently different than any pain the patient has experienced previously. These include shooting pain, numbness, cold, burning, and aching sensations. Some procedures in the brain can elicit more distress to the patient than the original pain. Spontaneous lesions can result in marked distortions of pain and pain-related symptoms (*see* Thalamic Syndrome, Chap. 23). The bizarre sensations perceived by an amputee in a phantom limb are expressions of processing within neural centers deprived of normal stimulation (*see* later). Destructive surgical lesions of the intralaminar and posterior

thalamic nuclei can alleviate intractable pain; in time, the pain might return.

Several surgical interventions suggest some functional roles for various regions of the brain: (1) Nociceptive information from one half of the body is conveyed to the same side of the spinal cord and then crosses over to the contralateral side to ascend as the neospinothalamic pathway to where aspects of perception occur in the thalamus and the somatosensory areas of the cortex. Painful stimuli can be perceived on the contralateral side of the body following ablation of the somatosensory cortex of a hemisphere. This is accomplished when the entire thalamus and other subcortical structures are intact. (2) The cortex of the frontal lobe and cingulate gyrus are involved in some way with the psychological responses to pain (Chap. 25), as are the dorsomedial and anterior thalamic nuclei with connections to the cortex of the frontal lobe (Chap. 22). Lesions of these nuclei, or of the nerve fibers linking them to the frontal lobe (called prefrontal leukotomy), lowers the agony associated with the persistent pain by altering the psychological response to the painful stimuli. The downside to this approach is the negative changes in the personality and intellectual status of the patient (Chap. 25). Bilateral severing of the fibers linking the cingulate gyrus to the frontal lobe (cingulotomy) can relieve the response to pain without the concomitant personality changes.

MAJOR CLASSES OF FUNCTIONALLY DEFINED NEURONS AND THE SPINOTHALAMIC TRACTS

Major Classes of Neurons in the Spinal Cord Associated with "Pain", and Ascending Projections

Lamina I contains three major classes of lateral spinothalamic tract neurons (**Figs. 9.1 and 9.4**). *Nociceptive-specific neurons (NS)* with small cutaneous receptive fields respond to noxious mechanical and/or thermal stimuli, but not to innocuous stimulation. In addition, they respond to noxious stimulation of muscles, joints, and viscera, *Polymodal nociceptive neurons (PC),* dominated by C fiber input, respond to noxious heat, cold, or pinch and also might respond to stimulation of muscles, joints, or viscera. *Thermoreceptive-specific neurons (COLD)* respond to innocuous cooling.

Laminae IV and V contain two major types of anterior spinothalamic tract cell. *Low-threshold cells (LT)* respond only to innocuous mechanical stimulation such as brushing (hair) or to both brushing and graded pressure. *Wide dynamic range nociceptive neurons (WDR)* respond to innocuous and noxious stimuli over fairly large cutaneous fields in a graded manner.

Functional Considerations

Studies of the anatomy of the pain system indicate that painful stimuli activate multiple pathways and, therefore, multiple nuclei, ganglia, and cortical areas of the forebrain, The processing nuclei assimilate past experiences and present context that collectively produce and result in the total multidimensional pain experience. These pathways and centers can contribute different aspects of pain sensation. The conscious pain–emotion content is constructed by the integration of contributions of the constellation of neural activity within the processing centers of the pain pathways.

Recent functional positron-emitting tomography (PET) and magnetic resonance imaging (MRI) investigations of the cerebrum have shown cortical areas that are activated by noxious heat and noxious cold stimuli, including the *primary* and *secondary somatosensory cortices*, lateral operculum (Chap. 25), *insula* and *anterior cingulate gyrus* ((*see* **Fig. 1.5**). Accompanying the perception of pain, PET activation has been observed in the periaqueductal gray, hypothalamus, amygdala, cerebellum, and some nuclei of the basal ganglia, structures that all receive some ascending nociceptive input.

Salient Features of the Spinothalamic and Trigeminothalamic Pain Pathways

The lateral spinothalamic tract pain and temperature system (LSTT; *see* **Fig. 9.2**) arises

from neurons called cold cells, polymodal nociceptive cells, and nociceptive-specific cells located in lamina I of the spinal cord that decussate and form the ascending LSTT. During its ascent into the thalamus, the tract emits collateral branches that terminate in parts of the brainstem reticular formation (Chap. 22) and the periaqueductal gray. Within the thalamus, fibers are distributed to several nuclei and their subdivisions, including the ventral caudal portion of the dorsomedial nucleus (DM), the ventral posterolateral nucleus (VPL), ventral posterior inferior nucleus (VPI), the central lateral and parafascicular intralaminar nuclei, and the posterior portion of the ventral medial nucleus (VMpo), part of the posterior thalamic group (*see* **Fig. 9.5**). In turn, DM projects to the base of the anterior cingulate gyrus; when activated, the sensation of burning pain can be felt. The densest LSTT terminations are in VMpo, which projects to the dorsal margin of the insula within the lateral fissure and is involved in "sensory representation of the physiological condition of the body" (lesions of this area have a minimal effect on the pain sensation) and in VPI, which also projects to the insula (activated by noxious heat or cold stimuli). Trigeminothalamic pain pathways are basically similar to the spinothalamic pain pathways except that fibers to the ventrobasal complex terminate in VPM rather than VPL (*see* **Fig. 9.6**).

The *anterior spinothalamic tract crude touch and movement sensation system (ASTT)* projects from neurons called wide dynamic range and low-threshold neurons in lamina 5) whose axons decussate and form the ascending ASTT (*see* **Figs. 10.3 and 10.4**). As the tract ascends, its collateral branches terminate in some brainstem reticular formation nuclei before terminating in the central lateral (CL) nucleus of the intralaminar nuclear group, VPL, and VPI. VPL projects somatotopically mainly to the primary somatosensory cortex (areas 3 and 1) and VPI projects mainly to secondary somatosensory cortex in the insula (Chap.25). The trigeminothalamic tracts have equivalent connections, which within the ventrobasal complex involve VPM. The functional roles of the pain pathways are subtlety influenced by the tracts and nuclei of the reticular system (ascending reticular activating system [ARAS], Chap 22). These include (1) the spinoreticular and spinomesencephalic tracts from the spinal cord (*see* **Fig. 9.2**) reticuloreticular and reticulothalamic tracts from the reticular formation of the brainstem, and the thalamocortical projections to the cerebral cortex and (2) nuclei such as the reticular nuclei of the brainstem and the CL and other intralaminar thalamic nuclei.

An insight into the intricacies of pain is provided by Craig and Dostrovsky (1999), who wrote "The most parsimonious and prospective view is that the activity of all of these ascending pathways must be integrated in the forebrain in the context of current conditions and past experience in order for all aspects of the sensation of pain to be generated." Elimination of a portion of the system or a given pathway, such as by a partial lesion in the periphery, in the spinal cord or in the forebrain, could cause an imbalance that could have variable effects on integrated sensation or in the central pain syndrome (*see* later). For example, it may result in pain without a noxious stimulus as in the phantom limb and central pain syndromes. These conditions emphasize the complexity of the spinal and supraspinal connections still to be identified that are involved in the experience of pain.

WALL'S CONCEPT OF PAIN IN TARGET MOTOR RESPONSES

"Pain for me arrives as a complete package," at the same time painful and miserable" (Wall and Melzack, 1999). Pain is also thought of as a subjective phenomenon perceived both as a sensation (cognitive) and as an affective (e.g., fear, miserableness) feeling tone. Thus patients suffering from intense pain and given morphine describe affect perceptions in the absence of cognitive pain. Other definitions are that pain is an abstraction of nociception or that pain is not a sensation, but a perception. Pain has been

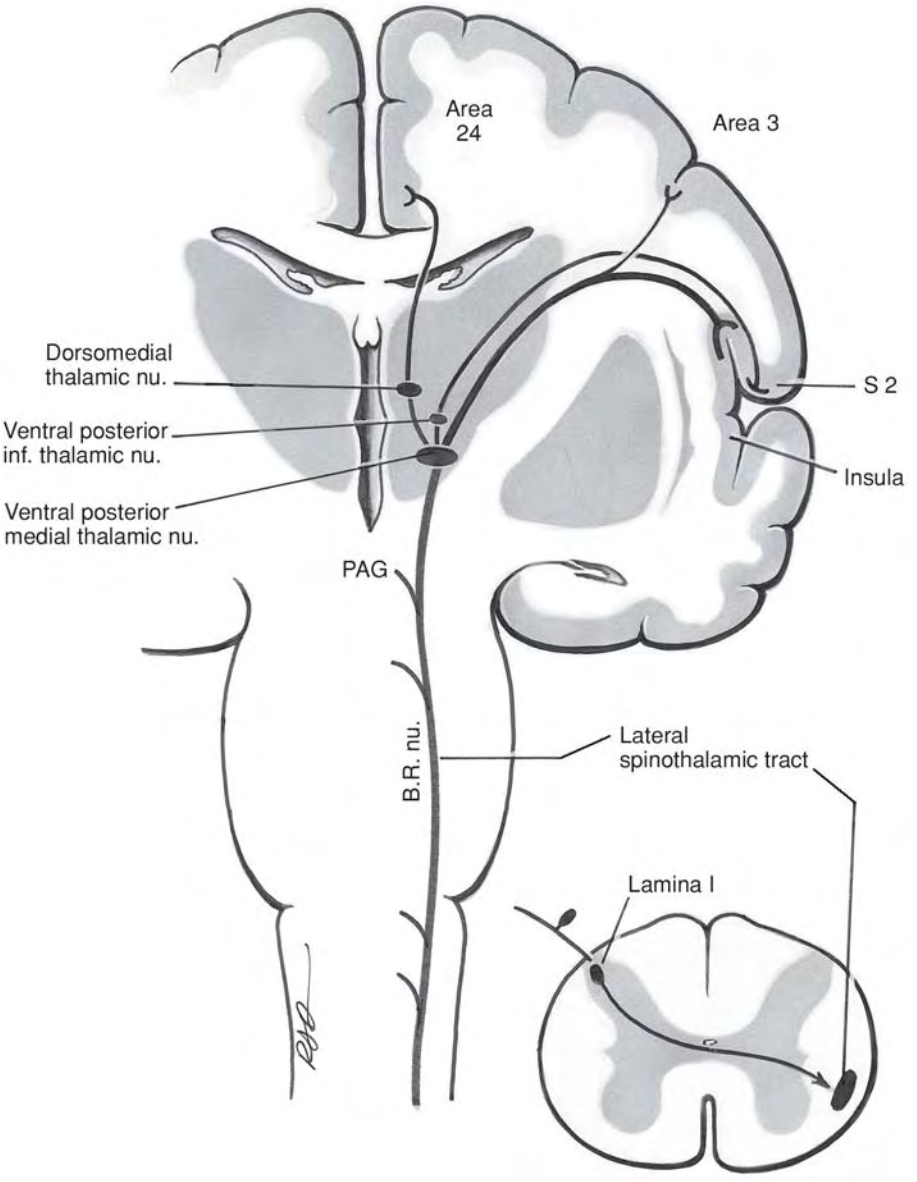


Figure 9.5: The ascending projections of the lateral spinothalamic tract (LSTT) activated by nociceptors and thermoreceptors of spinal cord lamina I neurons associated with the sensory modalities of *pain and temperature.* From cell bodies in lamina I, axons decussate in the anterior white commissure and ascend in the LSTT. Collateral branches synapse with nuclei of the brainstem reticular formation (RNu) and the periaqueductal gray (PAG; *see* Fig. 13.15). The main axons terminate at thalamic levels in the posterior zone of the ventral posteromedial nucleus (VMpo), the ventral posteroinferior (VPI), and the dorsomedial (DM) thalamic nuclei (*see* Table 23.1). In turn, these thalamic nuclei project to the secondary somatic sensory area (S2), insula (In), and anterior cingulate gyrus (area 24) of the cerebral cortex (*see* Figs. 25.3 and 25.6). Of significance is the sparse projection (thin line) to the primary somatic sensory cortex, area 3 (*see* Figs. 25.3 and 25.5). (Adapted from Craig and Dostrosky, 1999.)

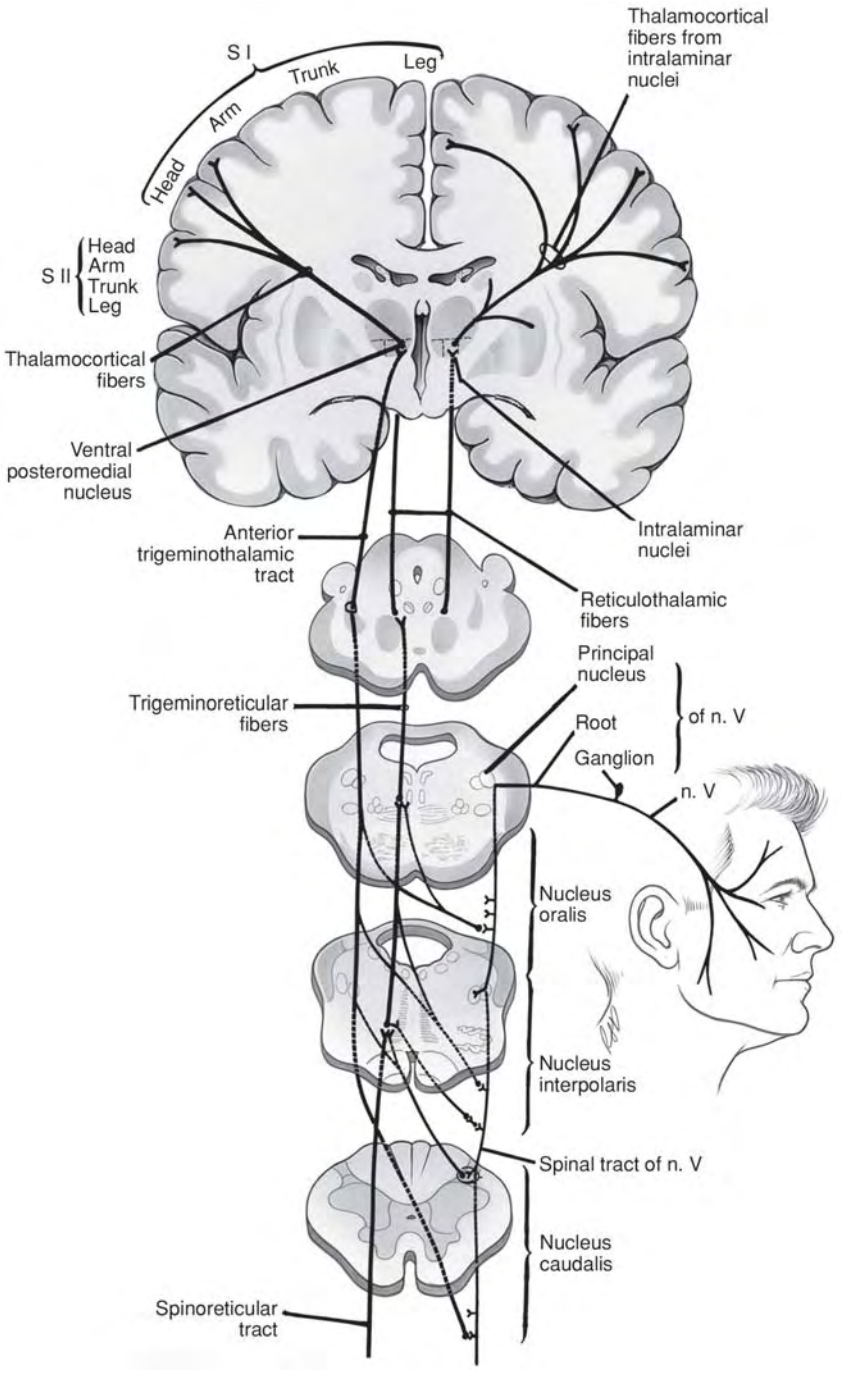


Figure 9.6: The pain and temperature pathways originating in the brainstem: the anterior trigeminothalamic tract and the trigeminoreticulothalamic pathway. Note that the ventral posteromedial thalamic nucleus projects to the head regions of both SI and SII of somatosensory cortex and that the intralaminar thalamic nuclei project diffusely and widely to the cerebral cortex. For details of structures in the brainstem sections, refer to the figures in Chap. 13.

conceived as a learned component with a *selection-attentive role* that commands and directs attention to only one target. When several pain sites burst out almost simultaneously, attention is directed to the "nothing else matters" one target and is followed by a directed motor response (e.g., withdrawal from the selected noxious target site).

There are two current concepts regarding the organization and purpose of the pain systems within the nervous system. (1) Some believe that pain can be adequately explained by the neural activity of dedicated pathway systems, which originate in peripheral pain receptors that result in the sensation of pain and elicit protective reflex response patterns. This traditional scheme commences with a stimulus followed by the conducting pathways to a combined memory–emotional response. (2) Others propose a more complex approach that takes into account the *plasticity* of all of the conducting pain pathways, involvement of successions of parallel processing centers (nuclei), basal ganglia, cerebral cortical areas, and even the cerebellum and, in addition, the active participation of the brain in perception.

In his discussion on the sensation of pain, Wall (Wall and Melzack, 1999), a premier authority, documents a new concept in answer to the question "How does the brain interpret input" with regard to "pain" stimuli?" The classical theory is that the brain analyzes the sensory input to determine what has happened and then presents the answer as a pure sensation. One among several objections to this theory is that the *primary somatic sensory cortex* (postcentral gyrus of the cerebral cortex Chap, 25), which has been assigned a key role in pain sensation analyses, often is silent in PET imaging studies although the subject reports pain.

The alternate concept proposed by Wall (Wall and Melzack, 1999) is that *"the brain analyzes its sensory input in terms of the possible action which would be appropriate to the event or which triggers the whole process."* Two critical items in this concept are (1) the *motor planning* that is appropriate to the event itself and (2) triggering the *motor movements* that result in the *target motor responses*. Convincing support for this alternate concept is derived from observations of PET scan images obtained from both normal subjects and patients with a variety of noxious pains. These high-resolution PET topographic images detect and map metabolic activities and reveal the localization of changes in the cerebral blood flow in certain brain areas and sructures. Studies of these PET scans led Wall (Wall and Melzack, 1999) to some of his reasoned interpretations.

PATHWAYS FROM THE ANTERIOR HEAD

Pain and temperature pathways from receptors in the head and scalp, anterior to a coronal plane through the ears, are the (1) trigeminothalamic and (2) trigeminoreticulothalamic tracts, both of which terminate in nuclei of the thalamus. These fibers convey impulses via the three divisions of the trigeminal nerve (ophthalmic, maxillary, and mandibular) and cranial nerves VII, IX, and X (*see* **Figs. 9.6 and 14.5**).

The cell bodies of the *first-order fibers* (A-delta and C fibers) are located in the trigeminal ganglion (V), the geniculate ganglion (VII), and the superior ganglia (IX and X). The fibers enter the brainstem and descend as the *spinal tract of n.V* (spinal trigeminal tract) on the lateral aspect of the lower pons, medulla, and upper two cervical spinal cord segments. The spinal trigeminal tract is somatotopically organized with fibers from the ophthalmic division most anterior, maxillary in an intermediate position, and mandibular division fibers together with those from nerves VII, IX, and X most posterior in the sequence; fibers from each of these nerves descend to the C2 level. They terminate in the *spinal nucleus of n.V*, which is located medial to the tract. The spinal tract and nucleus of n.V are the brainstem's counterpart of the posterolateral tract of Lis-

sauer and lamina I and II and deeper laminae of the spinal cord.

The spinal nucleus of n.V is a continuous structure that is subdivided into (1) the rostrally located *pars oralis* (nucleus oralis), which receives touch input from the mouth, lip, and nose, (2) the intermediately located *pars interpolaris* (nucleus interpolaris), which receives pain input from the tooth pulp (dental pain), and (3) the caudally located *pars caudalis* (nucleus caudalis), which receives pain, temperature, and light touch input from the face, mouth, and tooth pulp. The pars caudalis extends caudally to the C2 level (*see* **Fig. 9.5**).

From cell bodies in the spinal nucleus of n.V, *axons of second-order neurons* decussate through the lower brainstem reticular formation and ascend near the medial lemniscus as the *anterior trigeminothalamic tract* (anterior trigeminal tract) to terminate in the ventral posteromedial nucleus of the thalamus and in the posterior thalamic region. Axons of *third-order neurons* pass from the thalamus through the posterior limb of the internal capsule and corona radiata before terminating in the head region of the primary and secondary somatosensory cortices (SI and SII). The trigeminothalamic tract is included in the lateral pain system.

Diffuse, poorly localized pain from the head is probably conveyed by means of the *trigeminoreticulothalamic pathway*, in which fibers synapse within the reticular formation whose neurons project to the thalamic intralaminar nuclei (except the centromedian). The trigeminoreticulothalamic pathway is part of the medial pain system.

In summary, two pain and temperature pathways are recognized. They are called (1) the anterolateral and trigeminothalamic pathways and (2) the spinoreticulothalamic and trigeminoreticulothalamic pathways.

TEMPERATURE (THERMAL) SENSE

Free nerve endings are the peripheral receptors for the sensations of warmth and cold. Sensory inputs associated with these modalities are conveyed via lightly myelinated A-delta and unmyelinated C fibers. Cold is associated with both types of fiber and warmth is associated with C fibers. An intense heat stimulus can evoke the perception of cold, as can occur when one places a hand in hot water; this is called the *paradoxical cold sensation*. It results because heat does, at times, stimulate cold receptors. Although thermal pathways are virtually indistinguishable from those for pain, some researchers contend that the thermal senses are conveyed only by fibers of the anterolateral pathway and trigeminothalamic tract.

PERCEPTION OF PAIN

Pain is primarily a warning signal to the organism; it is often accompanied by withdrawal from a noxious stimulus via a flexor reflex. In a phylogenetic sense, pain must be one of the oldest protective responses of living organisms. The awareness of pain might be centered in the thalamus, as are certain associated aspects. For instance, a lesion of the dorsomedial nucleus can reduce the intensity or anguish of the pain experience. A lesion of the ventral posterior and intralaminar nuclei might relieve intractable pain, but in many patients, this is temporary, suggesting the existence of alternative pathways. Portions of the cortex seem to be important as well. The various nuances of pain (sharpness, dullness) seem to require activity of the secondary somatosensory area (SII). Portions of the parietal lobe appear necessary for a subject to locate the source of pain. On the other hand, large cortical ablation, including all of SI and SII, leaves chronic pain undiminished. The interplay of cortex and thalamus is uncertain, and some authorities conclude that the responses to a pain stimulus are indivisible. Dissociation between the perception and tolerance of pain has been noted following psychosurgical treatment of patients suffering from chronic pain. The surgery consists of a lobotomy of the prefrontal cortex (Chap. 24) or lesions of the dor-

somedial and anterior thalamic nuclei (nuclei having connections with the prefrontal cortex). These patients report the perception of the pain, but are no longer bothered by it.

Itching is related, in some unknown way, to pain. It originates from the stimulation of free nerve endings within or just deep to the epidermis of the skin. It is transmitted by C fibers and relayed to the brain via the anterolateral pathway.

THE GATE CONTROL THEORY OF PAIN MODULATION

A clinical method used to relieve pain (produce analgesia) is to stimulate the appropriate peripheral nerve with surface electrodes. The procedure is called *transcutaneous nerve stimulation* (TNS). An explanation for the success of this therapy is based on the gate control theory. In this concept, pain can be modulated by the balance of the interactions among the (1) *nociceptive C fibers* and (2) *non-nociceptive A-alpha* (proprioception) and *A-beta afferent* (touch) *fibers* of the peripheral nerves, and the (3) *interneurons* and (4) *projection neurons* of the dorsal horn. The latter are the neurons of the pain pathways (*see* **Figs. 9.3 and 9.4**).

The following describes the presumed actions of the neurons comprising the circuitry of the gate control model (*see* **Fig. 9.3**). The unmyelinated nociceptive C (pain) fiber inhibits the inhibitory interneuron and the projection neuron. The interneuron, which normally inhibits the projection neuron, is spontaneously active and, thus, reduces (inhibits) the intensity of the noxious input from the C fibers. The influences exerted by the spontaneous activity of the interneuron on the projection neuron are modulated by excitation from the non-nociceptive A fibers and inhibition from the nociceptive C fibers. In essence, nociceptive C fibers tend to keep the gate open (enhancing perception of pain) by inhibiting the inhibitory interneuron and exciting the projection neuron. The non-nociceptive A fibers tend to keep the gate closed (suppression of pain) by exciting the inhibitory interneuron. In addition, the reflected feedback descending influences from the brain can modulate the excitability of these neurons (*see* **Figs. 9.4 and 3.13**, and Chap. 10).

DESCENDING CONTROL MECHANISMS OF PAIN MODULATION (Fig. 9.4)

Pain and other sensory systems can be modulated and biased by influences conveyed from higher centers via descending tracts, known as *reflected feedback pathways* or *pain-modulating pathways* to lower levels of the ascending pathways. *Through* these connections, the sensitivity of receptors and processing centers can be enhanced or suppressed much like the gamma motor neurons modify the responsiveness of muscle spindles (Chap. 8).

The descending influences from higher centers modulating pain are organized in the following way. Output from the frontal cortex and hypothalamus activates centers in the PAG and adjacent areas of the midbrain, which have connections with tegmental nuclei of the rostromedial medulla (*see* **Fig. 9.4**). Another area involved with pain modulation is located in the tegmentum of the dorsal and dorsolateral pons. Fibers from these pontine and medullary tegmental nuclei project (1) to the spinal trigeminal nucleus, and (2) via the pain-modulating dorsolateral tract (located in the lateral funiculus adjacent to the dorsal horn) to laminae I and II of the spinal cord. Many of the neurons in the pons are adrenergic (contain norepinephrine), and those of the medulla are serotonergic (contain serotonin) (Chap. 15). Both of these biogenic amines have been implicated in pain modulation. The effect of the release of these biogenic amines and opioid peptides is that they bind to receptor sites and thereby suppress the activity of the "pain" neurons.

Opioid peptides and opiate drugs (e.g., morphine) are powerful analgesic agents. They produce analgesia by direct action upon specific receptor sites (opiate-binding receptors) on the

cell membrane of neurons. It is likely that the opioid-mediated analgesic system is activated by stress, pain itself, and suggestion. Certain neurons in the brain release neurotransmitters, called endogenous opioid peptides, that result in analgesia. Three families of these peptides are recognized: (1) enkephalins, derived from proenkephalin A, (2) beta-endorphin, from pro-opiomelanocortin (POMC), and (3) dynorphins, from prodynorphin. These opiates are presumed to be natural pain relievers because they ameliorate pain when microinjected into the PAG or into the superficial layers of the spinal cord. Endogenous opioid peptides are located in various structures in the CNS associated with transmission or modulation of pain. Enkephalins are located in the amygdala, hypothalamus, PAG, rostroventral tegmentum of the medulla, and dorsal horn of the spinal cord. Less widely distributed are beta-endorphins, located in the hypothalamus (arcuate nucleus), PAG, and in small amounts in the medulla and spinal cord. Dynorphin peptides are roughly similar to the enkephalins in their distribution.

ENDOGENOUS PAIN CONTROL

The natural variability of pain thresholds can be affected by the emotional state of an individual and by pharmacological agents such as aspirin and morphine. The control and modulation of nociception involves descending influences involving several descending neurotransmitter systems. Aspirin apparently acts peripherally, presumably by inhibiting transduction, and thereby minimizes the nociceptive signal. Aspirin is a true analgesic because it affects the entire sensation of pain. In contrast, morphine acts at synaptic sites in the CNS that reduce and modulate nociceptive signals. Morphine and other narcotics seem to mimic the effects of the endogenous opioids (Chap. 15).

The following pathway contributes to the control of nociceptive neurons in the spinal cord (*see* **Fig. 9.4**). Stimulation of the PAG of the midbrain (e.g., from the limbic system following a stressful episode such as a fire-fight in a battle) activates some of its neurons that descend and have excitatory synapses with serotonergic neurons in the nucleus raphe magnus and with groups of noradrenergic neurons in the reticular formation of the lower brainstem. The descending fibers from these neurons (1) directly inhibit the nociceptive projection neurons in the dorsal horn and (2) excite the enkephalin-containing interneurons in laminae I and II of the dorsal horn. These interneurons, through both presynaptic and postsynaptic connections, also inhibit the nociceptive projection neurons (*see* **Fig. 9.4**). Evidence indicates that endorphin-containing interneurons in both the PGA and dorsal horn are active in pain modulation.

REFERRED (TRANSFERRED) PAIN

Pain of visceral origin usually is vaguely localized. The site of visceral irritation and the locale where the pain is felt are not necessarily the same. The pain can be *referred* (transferred) from the visceral source to a corresponding dermatomal segment on the body, extremity, or head. *Referred pain* can also apply to pain from a somatic source.

The brain and the parenchyma of visceral organs do not have pain receptors. Such receptors are primarily in the walls of arteries, meninges, and all the pleural and peritoneal membranes. They are often the sources of severe pain when they are inflamed, irritated, or subjected to mechanical friction. Excessive contraction (cramps) or dilation (distention) of the body's hollow viscera (e.g., intestines) can also produce pain.

The following are examples of referred pain from visceral sources. The pain of coronary heart disease can be referred to the chest wall, left axilla, and the inside of the left arm. The spinal cord segments T1 and T2 innervate the heart and the skin (dermatomes) areas of the chest, axilla, and left arm. An inflammation of the peritoneum on the diaphragm (often related to the gallbladder) can be referred to the shoulder region. Spinal segments C3–C5 supply sen-

sory as well as motor innervation to the diaphragm (via the phrenic nerve) and, in addition, to the shoulder region. The source of headaches is not the brain *per se*. Headaches are thought to be referred from irritated nerve endings in the intracranial (meningeal) and other blood vessels.

A somatic source of referred pain is from the back. The sources of the pain can be receptors associated with the ligaments and muscles attached to the bony vertebral column. The pain is often referred to a different spinal level.

One concept to explain the phenomenon of referred pain is based on the demonstration that nociceptive fibers conveying information from a cutaneous source and those from a visceral source can converge within the same projection neuron pool in the dorsal horn. The projection neurons of the pain pathways receiving these dual inputs project to higher centers, which cannot discriminate the precise source. The pain often is incorrectly attributed to the skin, which is normally the source of greater nociceptive input.

STIMULUS-INDUCED AND STRESS-INDUCED ANALGESIA

Severely wounded soldiers, athletes injured in sports, and professional boxers state that they do not feel pain during and even just after the stressful events of combat. During a race, marathon runners undergo the feeling of "running through pain". Electric stimulation of the periaquaductal gray in humans produces a drastic reduction in clinical pain, called stimulus-induced analgesia. Patients describe a pain that fades away over a few minutes, and even a feeling of warmth and relaxation. The stimulation presumably activates the pain-modulating networks, including the biogenic amine analgesic system and the opioid-mediated modulating system.

The ability to respond during emergency situations and to stress by suppressing or reducing the sensitivity to pain is known as behavioral stress-produced analgesia. It is likely that pain stimuli evoke some of this response via pathways from the frontal cortex, limbic system, and hypothalamus that activate the nonopiate biogenic amine analgesic system and the opiate-mediated analgesic system to suppress the sensation of pain.

Conceptually, the withdrawal reflex is a response of drawing back from a noxious stimulus and the pain sensation correlated with the reflex. In this respect, pain reflex withdrawal is a normal reaction to protect the organism, and the analgesic systems are the organism's means of controlling the pain system.

CENTRAL PAIN SYNDROME (THALAMIC SYNDROME)

Injury involving the lateral spinothalamic tract system or trigeminothalamic tract system can result in the *central pain syndrome* characterized by spontaneous, often excruciating burning pain (causalgia) in the region of the head, limbs, or body represented by the damaged tract. Other effects of the lesion are discussed in Chapters 12 and 17. Such lesions can occur in such locations as the cerebral cortex, thalamus, brainstem, and spinal cord. Stimulation of anesthetic areas in the periphery can elicit the central pain syndrome.

A lesion (e.g., produced by a stroke) in VPL and VPM and the adjacent corticospinal tract in the internal capsule produces a central pain syndrome called the *thalamic syndrome*, characterized by hemianesthesia and an upper motor neuron paralysis on the opposite side (Chaps. 12 and 17). Numerous explanations have been advanced to explain the causes of the symptoms of the thalamic syndrome (Chap. 23).

PHANTOM LIMB SENSATION

The phantom limb is an expression of activity in nuclei deprived of normal stimulation. An amputee might feel diffuse pain in an amputated extremity. The phantom limb "moves" easily, even through objects and the

remaining limb. The wristwatch, formerly worn, might still be felt on a nonexistent wrist. An explanation is that the nuclear complexes that previously received input from the phantom limb are still present in the nervous system; when these complexes are stimulated in some way, they set in motion neural activities that produce sensations felt as though coming from the absent limb.

SOMATOTOPIC ORGANIZATION OF THE LATERAL SPINOTHALAMIC TRACT

The laminated, somatotopic organization of the lateral spinothalamic tract, with fibers from successively higher levels being located anteromedial to those from lower levels, has significance in analyzing distributions of pain sensation (*see* **Fig. 7.6**). Pressure on the lateral aspect of the cervical spinal cord (e.g., from an extramedullary tumor) would interrupt pain and temperature fibers from the contralateral sacral region first and then, as the tumor enlarges, those from lumbar, thoracic, and cervical regions. A lesion in the middle of the spinal cord surrounding the central canal in the region of the cervical enlargement (e.g., as in syringomelia) would interrupt pain and temperature fibers that results in the loss of pain and temperature bilaterally in both upper extremities (Syringomelia, Chap.12).

SUGGESTED READINGS

Andrew D, Craig AD. Spinothalamic lamina I neurons selectively sensitive to histamine: a central neural pathway for itch. *Nature Neurosci.* 2001;4:72–77.

Basbaum AI. Distinct neurochemical features of acute and persistent pain. *Proc. Natl. Acad. Sci. USA* 1999;96:7739–7743.

Basbaum AI, Woolf CJ. Pain. *Curr. Biol.* 1999;9: R429–R431.

Beecher H. Pain in man wounded in battle. *Ann , Surg.* 1944;123:96–105.

Beggs J, Jordan S, Ericson AC, Blomqvist A, Craig AD. Synaptology of trigemino- and spinothalamic lamina I terminations in the posterior ventral medial nucleus of the macaque. *J. Comp. Neurol.* 2003;459:334–354.

Blomqvist A, Zhang ET, Craig AD. Cytoarchitectonic and immunohistochemical characterization of a specific pain and temperature relay, the posterior portion of the ventral medial nucleus, in the human thalamus. *Brain* 2000;123(Pt. 3): 601–619.

Craig AD. Pain mechanisms: labeled lines versus convergence in central processing. *Annu. Rev. Neurosci.* 2003;26:1–30.

Craig AD, Dostrovsky JO. Medulla to thalamus. In Wall PD, Melzack R, editors. Textbook of pain. New York: Churchill Livingston; 1999:183–214.

Craig AD, Bushnell MC, Zhang ET, Blomqvist A. A thalamic nucleus specific for pain and temperature sensation. *Nature.* 1994;372:770–773.

Dubner R, Gold M. The neurobiology of pain. *Proc. Natl. Acad. Sci. USA* 1999;96:7627–7630.

Fields HL. Pain modulation: expectation, opioid analgesia and virtual pain. *Prog. Brain Res.* 2000;122:245–253.

Iggo A. Sensory receptors in the skin of mammals and their sensory functions. *Rev. Neurol. (Paris)* 1985;141:599–613.

Ito S, Craig AD. Vagal input to lateral area 3a in cat cortex. *J Neurophysiol.* 2003;90:143–154.

Julius D, Basbaum AI. Molecular mechanisms of nociception. *Nature.* 2001;413:203–210.

Light AR, Perl ER. Unmyelinated afferent fibers are not only for pain anymore. *J. Comp. Neurol.* 2003;461:137–139.

Loeser JD, Bonica, JJ, eds. *Bonica's Management of Pain.* 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001.

Melzack R. Phantom limbs. *Sci. Am.* 1992;266: 120–126.

Melzack R. Pain and the neuromatrix in the brain. *J. Dent. Educ.* 2001;65:1378–1382.

Mitchell JM, Basbaum AI, Fields HL. A locus and mechanism of action for associative morphine tolerance. *Nature Neurosci.* 2000;3:47–53.

Potrebic S, Ahn AH, Skinner K, Fields HL, Basbaum AI. Peptidergic nociceptors of both trigeminal and dorsal root ganglia express serotonin 1D receptors: implications for the selective antimigraine action of triptans. *J. Neurosci.* 2003;23: 10,988–10,997.

Price DD, Greenspan JD, Dubner R. Neurons involved in the exteroceptive function of pain. *Pain* 2003;106:215–219.

Saab CY, Willis WD. Nociceptive visceral stimulation modulates the activity of cerebellar Purkinje cells. *Exp. Brain Res.* 2001;140:122–126.

Saab CY, Willis WD. The cerebellum: organization, functions and its role in nociception. *Brain Res. Brain Res. Rev.* 2003;42:85–95.

Wall PD, Melzack R. *Textbook of Pain.* 4th ed. New York: Churchill Livingstone; 1999.

Wall PD, Melzack R. *Handbook of Pain Management.* New York: Churchill Livingstone; 2003.

Willis WD, Westlund KN. Neuroanatomy of the pain system and of the pathways that modulate pain. *J. Clin. Neurophysiol.* 1997;14:2–31.

Willis WD, Al Chaer ED, Quast MJ, Westlund KN. A visceral pain pathway in the dorsal column of the spinal cord. *Proc. Natl. Acad. Sci. USA* 1999; 96:7675–7679.

Willis WD, Jr., Zhang X, Honda CN, Giesler GJ, Jr. Projections from the marginal zone and deep dorsal horn to the ventrobasal nuclei of the primate thalamus. *Pain* 2001;92:267–276.

Willis WD, Jr., Zhang X, Honda CN, Giesler GJ, Jr. A critical review of the role of the proposed VMpo nucleus in pain. *J. Pain.* 2002;3:79–94.

10
Discriminative General Senses, Crude Touch, and Proprioception

Somatosensory Receptors (Mechanoreceptors)
Pathways Serving the Discriminative General Senses and Proprioception
Pathways Serving Crude (Light) Touch and Movement Sensation
Proprioceptive Pathways of the Head
Proprioceptive Pathways to the Cerebellum
Functional Correlations

Touch and the discriminative general senses encompass a number of sensory modalities. Touch by itself refers to *crude* (also called *light*) and movement sensation, which yields little information apart from the fact of contact with an object. The discriminative general senses (DGS) also include the following: "pressure touch," which enables an awareness of shape, size, and texture; *stereognosis*, appreciation of an object's three dimensionality; perception of an object's weight; vibratory sense (as tested with a tuning fork); position sense (awareness of body parts, especially joints); and awareness of body and limb movement, including direction. The last two are often grouped as *kinesthetic sense*.

These modalities are monitored by exteroceptors located in the surface layers of the skin and oral mucosa and by proprioceptors located in the deeper skin layers, joint capsules, ligaments, tendons, muscles, and periosteum. With the proviso that the correlation of a specific modality of sensation with a morphologically identifiable nerve ending is not completely conclusive, it is possible to assign the following receptors to modalities.

SOMATOSENSORY RECEPTORS (MECHANORECEPTORS)

Four types of somatosensory receptor are located in the skin and subcutaneous tissues. Mechanoreceptors are encapsulated nerve endings named Meissner, Ruffini, and Pacinian corpuscles and Merkel disks (*see* **Figs. 10.1 and 10.2 and Table 7.3**). The mechanical transduction (mechanotransduction), from the application of stimuli to these receptors to the generation of action potentials in the sensory neurons, is conventionally viewed as a three-stage process: (1) The stimulus (touch or movement) is mechanically applied to the cells encapsulating the receptor nerve ending; (2) the deformation is transduced into an electrical signal), the receptor (generator) potential; (3) the receptor potential is encoded into action potentials (at first node of Ranvier) for transmission by the sensory neuron to the central nervous system (CNS). Each receptor can be characterized by the quality of the modality perceived, size of receptive field, stimulus threshold, speed of adaptation, and the first-order fiber type projecting to the CNS.

The *receptive field* is the region of skin capable of activating a receptor. The *stimulus threshold* is the intensity level required to activate the receptor. *Adaptation* is the response and adjustment a receptor makes to a stimulus. Some receptors generate action potentials when the stimulus starts and then soon ceases to respond. This type of receptor, called a *rapidly adapting receptor,* provides information primarily when a stimulus changes. When an object (e.g., clothes) touches our skin, we soon

become unaware of the object because the reacting sensors are rapidly adapting receptors. Other receptors that continue to respond as long as the stimulus is applied are called *slowly adapting receptors*. Such receptors include nociceptors that are responsible for the warning that is the perception of pain.

Merkel disks respond to steady skin indentation from a tactile stimulus. Each has a large receptive field and is a *slowly adapting receptor*. *Meissner corpuscles* are associated with the tactile sense called fluttering (felt as a gentle trembling of the skin). Each has a large receptive field and is a rapidly adapting receptor. *Merkel disks* and *Meissner corpuscles* have large fields and are rapidly adapting receptors. The *Pacinian corpuscle* is involved with vibratory sense (felt as a diffuse humming sensation). Vibratory sense is poorly localized because Pacinian corpuscles have large receptive fields. In addition, they are rapid adapting receptors. Pacinian corpuscles

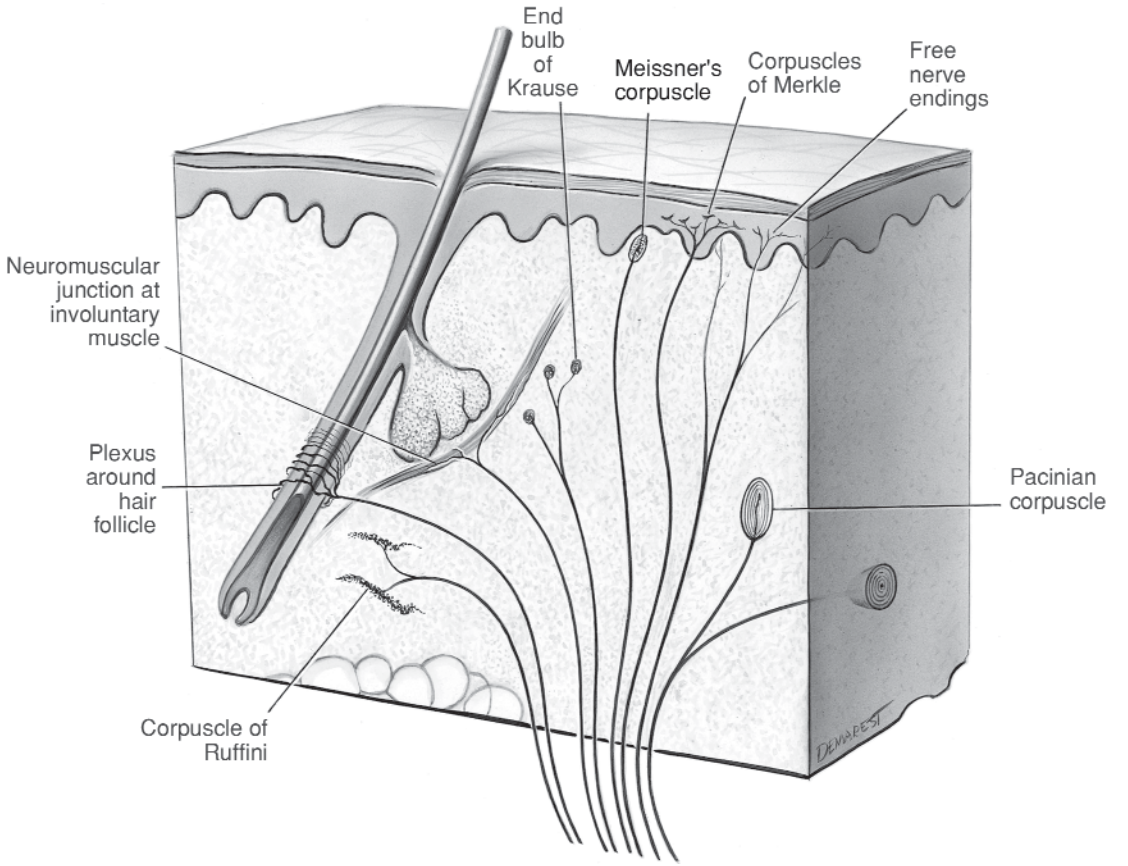


Figure 10.1: Sensory nerve endings in the skin. Receptors located in the epidermis include free nerve endings associated with pain and thermal sense and Merkel's corpuscles, activated by steady skin indentation—a form of touch. Receptors located in dermal papillae, at the junction of the dermis and epidermis, are Meissner's corpuscles, which monitor touch, especially sensing fine spatial differences. The hair receptors (plexus around each hair follicle) subserve tactile sense and flutter. Receptors located in the dermis are the pacinian corpuscles and corpuscles of Ruffini. Pacinian corpuscles are involved with sensing deep pressure and vibration. The corpuscles of Ruffini and a variant called the end bulbs of Krause subserve touch pressure and vibratory sense.

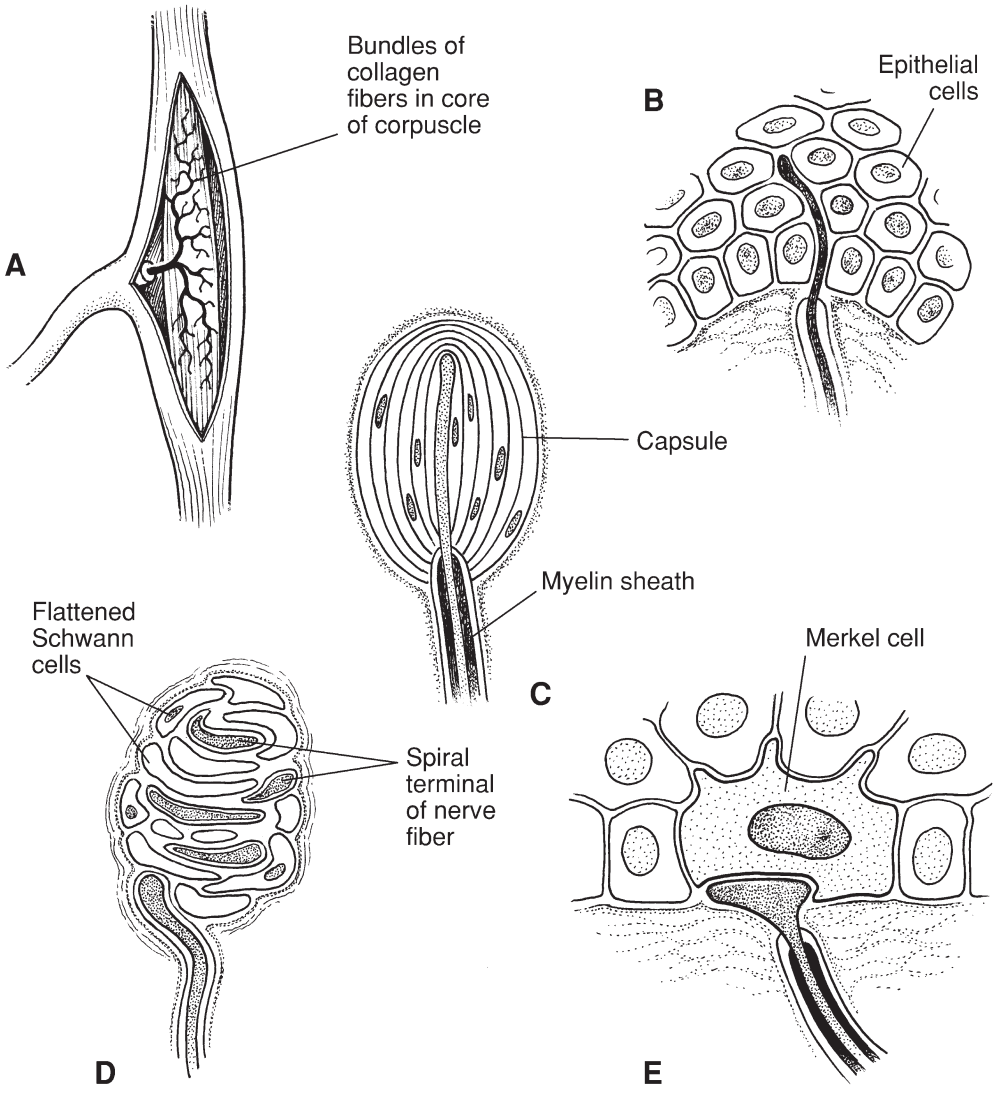


Figure 10.2: Sensory receptors of the skin. **(A)** Corpuscle of Ruffini, an encapsulated receptor, is supplied by a single myelinated axon that branches repeatedly to form diffuse unmyelinated terminals among bundles of collagen fibers in the core of the capsule. These terminals are presumably stimulated by the displacement of the collagen fibers among which they are intertwined. Modified Schwann cells are absent. **(B)** Free nerve endings in the epidermis where they lie between contiguous epithelial cells. **(C)** Pacinian corpuscle, an encapsulated receptor, is innervated by a single myelinated axon that extends as an unmyelinated ending through the center of the bulb. The flattened cells surrounding the axon in the core of the capsule are presumably modified Schwann cells. **(D)** Meissner's corpuscle, an encapsulated receptor, is innervated by a myelinated axon that forms an unmyelinated spiral ending amid flattened transversely oriented Schwann cells. **(E)** Merkel's corpuscle is a modified epidermal cell located in the basal layer of the epidermis. It is innervated by a myelinated nerve fiber "synapsing" as a free nerve ending with a Merkel's cell. (Adapted from Cormack, 1987).

are also located in the connective tissues of mesenteries, muscles, and interosseous membranes. *Ruffini corpuscles* are associated with the sense of touch pressure and vibratory sense. These corpuscles are of significance to the blind in "reading Braille" because they have small receptive fields and adapt rapidly, enabling them to resolve fine spatial differences quickly. Each of these four receptor types has a low stimulus threshold and conveys information to the CNS via A-beta nerve fibers of first-order neurons. Of the rapidly adapting receptors, the polymodal nociceptors of free nerve endings can act as somatosensory receptors (Chap. 9).

Receptors, especially muscle spindles and Golgi tendon organs (GTOs), are continuously monitoring the degree of muscle contraction and tension within the tendons (Chaps. 8 and 11). The resulting "unconscious proprioception" is utilized in reflex arcs and by many processing centers, especially the cerebellum. It is now recognized that signals from spindles and GTOs are also integrated into the lemniscal system and contribute to the conscious appreciation of position and movement sense.

The major somatic modalities elicited by mechanoreceptors are (1) *tactile sensations* evoked by the application of mechanical stimuli to the body surface and (2) *proprioceptive sensations* evoked by the mechanical displacements of muscles, ligaments, and joints. *Proprioception* is the sense of balance, position, and movement.

The two types of tactile sensation are *crude (light) touch* and *tactile discrimination. Crude touch* is that felt by lightly stroking the skin with a wisp of hair or cotton. It can be tested by having an individual, with eyes closed, identify the location of a touch. *Tactile discrimination* or *pressure touch* is often called *two-point discrimination*, which is the ability to distinguish two separate loci where two points (e.g., a pin) are applied to the skin; spatial resolution is directly related to receptor density and is very fine at the fingertips. Tactile discrimination is also expressed as the ability to localize and to perceive the shape, size, and texture of an object by palpation, otherwise known as *stereognosis*. Proprioception takes on various forms, including vibratory sense, static proprioception, and dynamic proprioception. *Perceiving vibrations when the stem of a vibrating tuning fork is placed on a joint or other body part can test vibratory sense*. *Static proprioception* is expressed as the ability to sense the position of a body part from information received from that part (called *position sense*). *Dynamic proprioception* or *kinesthetic sense* is the ability to sense movement and balance.

PATHWAYS SERVING THE DISCRIMINATIVE GENERAL SENSES AND PROPRIOCEPTION

DGS Pathway From the Body, Limbs, and Back of Head

The primary role of the DGS pathway is to convey, in response to stimuli, neural information associated with kinesthetic sense and stereognosis. The latter is a complex sense that is based on such qualities as location, spatial form, and the sequence of inputs over time: The integration of these qualities results in the perception of form and shape of objects that are touched, felt, and held in hand. In addition, (1) the trigeminothalamic pathway responds to similar stimuli from the rest of the head, (2) the *lateral cervical system* (also called the spin cervical tract) responds to certain touch and DGS stimuli, and (3) the anterior spinothalamic pathway is involved in mediating crude touch and movement sensations (*see* **Figs. 10.3, 10.6, and 10.7**).

The DGS pathway is serially organized as a basic sequence of *three* orders *of neurons* conveying information to the cerebral cortex. Information from the body, limbs, and back of the head (scalp posterior to the coronal plane through the ears) is conveyed from the peripheral receptors over *first-order neurons* of the spinal nerves with cell bodies in the dorsal root ganglia (Features of Sensory Systems, Chap. 9). Their heavily myelinated fibers enter the spinal cord as the *medial bundle of the dorsal roots* (*see* **Figs. 10.3 and 10.4**) and branch into

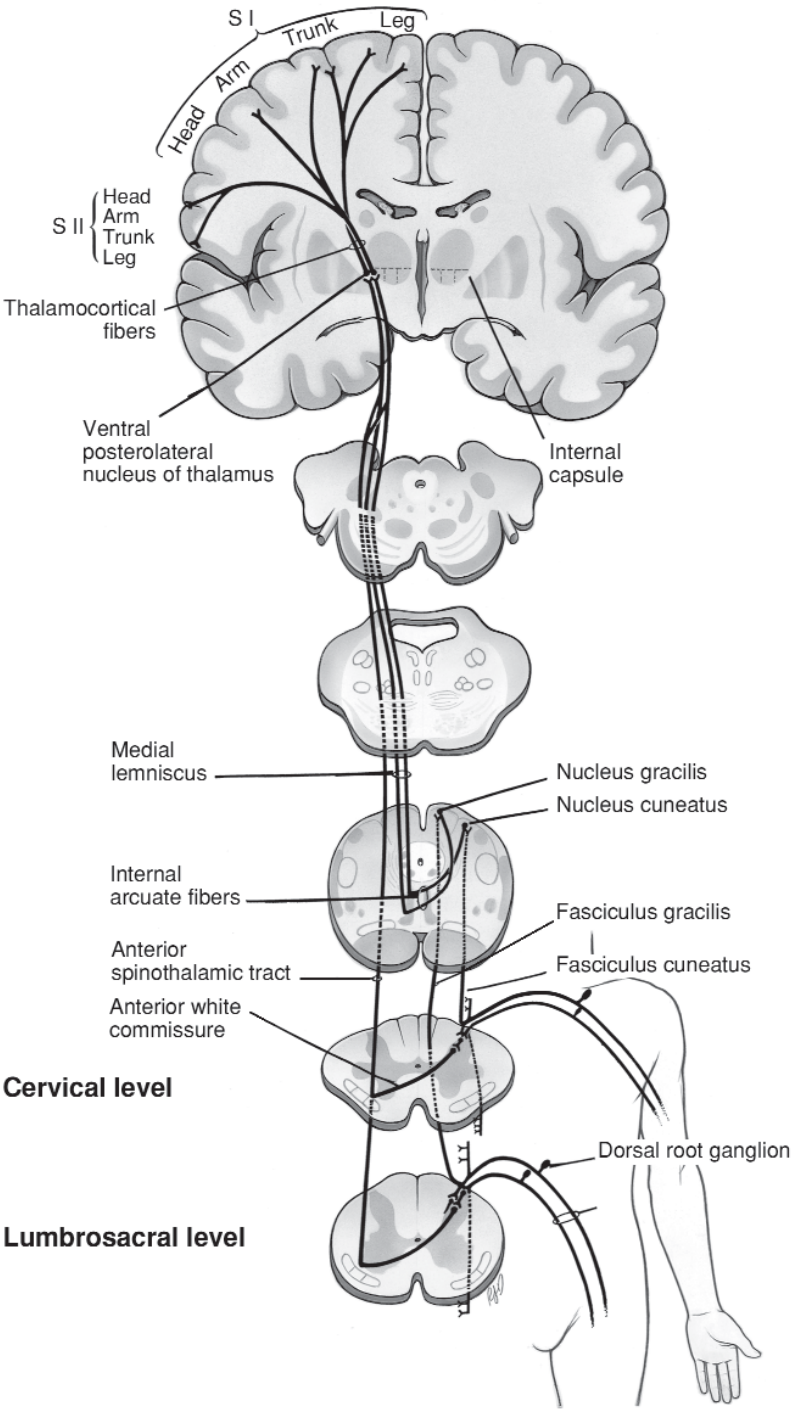


Figure 10.3: The discriminatory general sensory pathways originating in the spinal cord comprise the posterior column–medial lemniscus pathway and the anterior spinothalamic tract. Note that the ventral posterolateral (VPL) thalamic nucleus projects to body regions of both SI and SII.

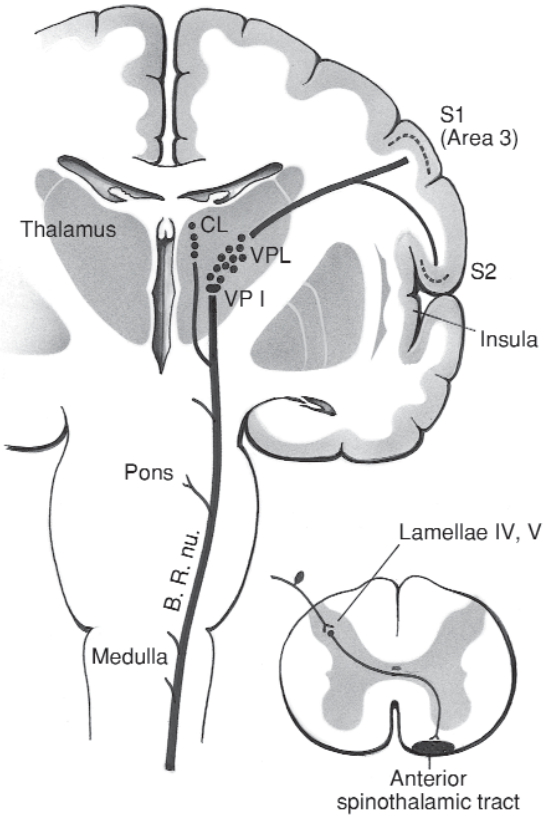


Figure 10.4: The ascending projections of the anterior spinothalamic tract. Receptors mediating *crude touch and movement sensations* are innervated by fibers that terminate in the dorsal horn of the spinal cord. Axons arising from cell bodies located in the dorsal horn decussate in the anterior white commissure and ascend in the anterior quadrant of the spinal cord as the anterior spinohalamic tract crude touch and movement sensation system (ASST); collateral branches terminate in brainstem reticular nuclei B.R.nu). The main axons terminate in the ventral posterior inferior nucleus (VPI), ventral posterolateral nucleus (VPL), and central lateral (CL) nucleus of the intralaminar group of thalamic nuclei (Chap. 22). VPI and VPL thalamic nuclei project to primary (S1) and secondary (S2) somatic sensory cortex (Fig. 25.3). IV and V, spinal cord laminae IV and V, respectively; S1 (area 3), primary somatic sensory cortex; S2, secondary somatic sensory area. (Adapted from Craig and Dostrosky.)

(1) collaterals, which terminate mainly in laminae III and IV of the posterior horn and (2) fibers that ascend in the ipsilateral *fasciculi gracilis* and *cuneatus* of the dorsal (posterior) column before terminating in the *nuclei gracilis* and *cuneatus* of the lower medulla. Some of the collaterals ending in the posterior horn synapse with interneurons involved with spinal reflex arcs (Chap, 8).

The ascending axons of the *dorsal column–medial lemniscus pathway* exhibit a somatotopically organized lamination according to body area innervated (*see* **Fig. 7.6**). Fibers are added to the lateral aspect of the dorsal column (fasciculi gracilis and cuneatus) at each successively higher spinal cord level. The medial–lateral lamination at upper cervical levels consists, in sequence, of fibers from sacral, lumbar, thoracic, and cervical segments of the body. Fibers from the sacral, lumbar, and lower six thoracic levels compose the *fasciculus gracilis* of the posterior column and those of the upper six thoracic and all cervical levels (includes innervation of the back of head) form the *fasciculus cuneatus*. The fibers terminating in the nucleus gracilis originate from below T6 (including the lower extremity); those terminating in the nucleus cuneatus originate from above T6, including the upper extremities. The proprioceptive fibers from the lower extremity ascend in the dorsolateral fasciculus (located dorsally in the lateral column between the posterior gray horn and the posterior spinocerebellar tract; *see* **Fig. 7.6**) with the fibers of the lateral cervical system to the lateral cervical nucleus (*see* later). Following neural processing within the nucleus gracilis and nucleus cuneatus information is projected to the *ventral posterolateral (VPL) nucleus of the thalamus*. The processing within the posterior column nuclei *consists* of both feedback inhibition and feed-forward inhibition and, in addition, modulation by distal (reflected) inhibition from the cerebral cortex (Chap. 3; *see* **Fig. 3.13**). The axons of *second-order neurons* that emerge from the nuclei gracilis and cuneatus arc anteriorly as the *internal arcuate fibers*, decussate in the lower medulla, ascend as the

somatotopically organized *medial lemniscus,* and terminate in the VPL nucleus of the thalamus. As it ascends, the medial lemniscus gradually shifts from a medial location in the medulla to a posterolateral location in the upper midbrain.

Thalamus and Somatic Sensory (Somatosensory) Cortex. The *VPL* thalamic nucleus receives sensory input from the body via fibers of the medial lemniscus and spinothalamic tract, which terminate in a somatotopic pattern. VPL is parceled functionally as follows: The *central core* of the nucleus is responsive to stimuli from cutaneous receptors; the surrounding *shell* is responsive to stimuli from deep receptors (e.g., muscle spindles) (*see* **Fig. 10.5**). In addition, VPL receives reflected (distal) inhibitory influences from somatosensory cortex. Axons of third-order neurons emerge from VPL, pass through the posterior limb of the internal capsule and corona radiata, and terminate in lamina IV of the somatosensory cortex of the parietal lobe, located in the postcentral gyrus and in the adjacent paracentral lobule on the medial surface of the hemisphere (Organization of Neocortex, Chap. 25). The somatic sensory cortex consists of the *primary somatosensory cortex* (SI; areas 1, 2, 3a, and 3b), *secondary somatosensory cortex* (SII) (both located in the postcentral gyrus), and the posterior parietal cortex (areas 5 and 7).

The somatotopic representations of the body surface are present in the cortex in an orderly manner, but with the cortical receptive field size of the two homunculi of the primary and secondary somatosensory cortices roughly proportional to the resolution of stimuli from regions of different densities of receptors (e.g., skin); one each for areas 1, 2, 3a, and 3b of SI and one for SII (*see* **Fig. 25.4**) The receptive field sizes are directly related to the density of receptors on the body. The back with a low density of receptors has a small cortical representation compared to the much larger cortical representation of the fingertips, which have a high density of receptors.

There are somatotopic projections (1) from the medial lemniscus and spinothalamic tracts to the VPL nucleus and (2) from the core and shell of VPL to somatosensory cortex (areas 1, 2, 3a, and 3b) (*see* **Fig. 10. 5**). (1) The *core neurons* receive cutaneous input from slow and rapidly adapting receptors involved with the discrimination of texture. The third-order thalamic neurons of the core receiving inputs from these receptors have substantial projections that terminate in area 3b. Those thalamic neurons of the core receiving inputs from rapidly adapting receptors involved with sensing texture have sparse projections that terminate in areas 1, 3b, and SII. (2) The *shell neurons* receive inputs from the deep tissue receptors monitoring muscle stretch, deep pressure, and joint sense. Those thalamic neurons of the shell receiving inputs from muscle spindle stretch receptors have substantial projections that terminate in area 3a. Those thalamic neurons of the shell receiving stimuli from deep pressure and joint receptors involved with sensing size and shape of objects held in the hand have sparse projections that terminate in areas 3a, 2, and SII. In turn, neurons from areas 3a and 3b project to areas 1 and 2 and all four areas project to SII, which is involved in the discrimination of shape, size, and texture. All five areas of SI and SII have connections with parietal lobe association areas 5 and 7 (Chap. 25).

A similar structural and functional organization is expressed in the ventral posterior medial (VPM) thalamic nucleus, which is the nucleus receiving somatosensory input from the head primarily from the trigeminal nerve (*see* **Figs. 10.6, 14.5, and 23.3**). The VPM nucleus receives input from the trigeminothalamic pathways and projects to the head region of the somatosensory cortex.

The Paths From Receptors to Columns of the Cortex. The sensory pathways involved with sensation are composed of sequences of neurons forming paths transmitting labeled line codes and pattern codes. The lemniscal and trigeminal pathways consist primarily of projections extending from the somatic receptors in the body to functional columns (slabs) in the

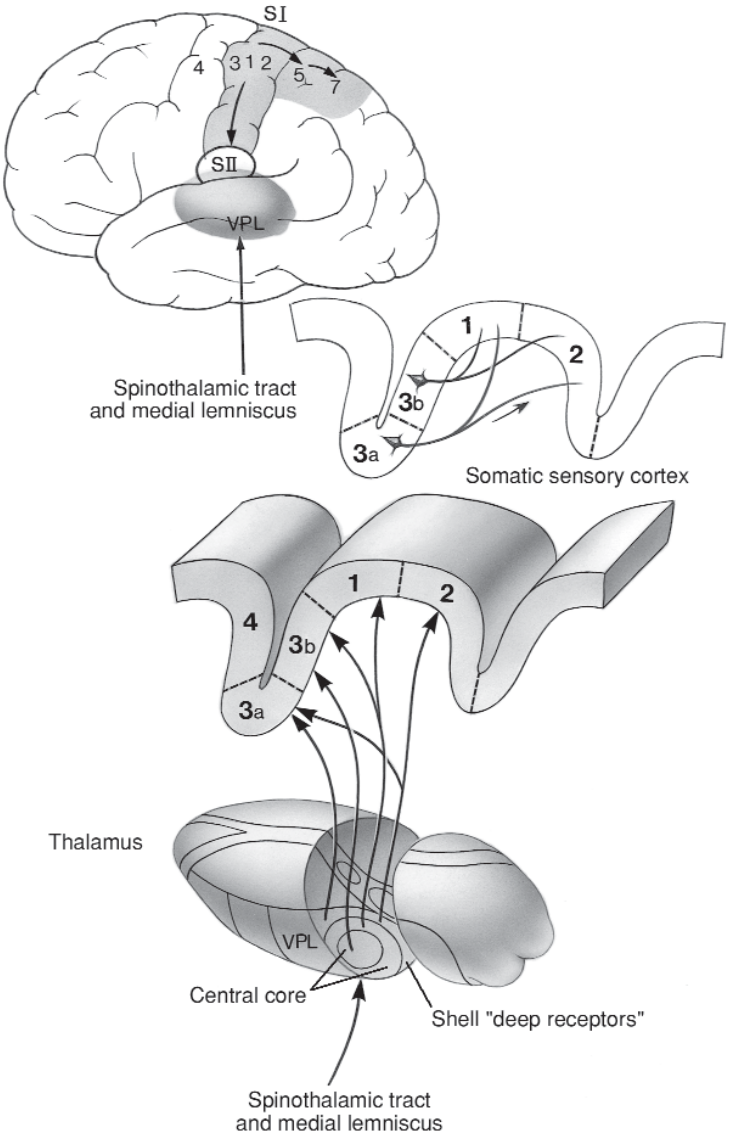


Figure 10.5: Schema illustrating the projections from the ventral posterior lateral (VPL) and ventral posterior medial thalamic (VPM) nuclei to somatosensory cortex. VPL receives input from the medial lemniscus and spinothalamic tracts, and VPM receives input from the trigeminothalamic tracts. These nuclei are organized into a central core consisting of two zones, each responsive to cutaneous stimuli, and an outer shell responsive to deep stimuli. Neurons of the central core project to cortical areas 3b and 1 (cutaneous). Neurons of the outer shell project to areas 3a (muscle spindles) and 2 (deep receptors). These projections are somatotopic.

The somatosensory cortex of the parietal lobe consists of three major subdivisions: primary somatosensory cortex (SI of areas 3, 1, and 2), secondary somatosensory cortex (SII of areas 3, 1, and 2), and posterior parietal cortex (areas 5 and 7). Neurons in areas 3a and 3b project to areas 1 and 2. Neurons of SI (areas 3a, 3b, 1, and 2) project to the secondary sensory cortex (SII). Neurons from SI and SII and some thalamic neurons project to area 5, and the latter to area 7. (Adapted from Carpenter and Sutin, 1983.)

postcentral gyrus of the parietal lobe (Chap. 25). Each receptor exhibits specificity, in that it responds to specific stimulus energy. Each line conveys a specific stimulus quality (e.g., position sense) and processes the message in each nucleus of the pathway before arriving for more processing in a cortical column. The stimulus feature encoded by a receptor in the body is faithfully reproduced by the signal received by that line in the cortex. For example, slowly adapting receptors are coupled to slowly adapting neurons of the thalamus that are sequentially coupled with slowly adapting neurons in a column of areas 3a and 3b of the somatosensory cortex. It is of significance that all six layers in each cortical column represent the same modality. Thus, many lines transmitting different features of each sensation are paths where parallel processing of the stimulus features occurs. It is in the highest centers in the cortex that the features are integrated into a sensation. The paths are not redundant because they accent different features. Parallel processing of stimulus features in several lines has a significant role in the generation of the variety and subtleties associated with perceptions.

Trigeminothalamic Pathway From the Facial Region

The discriminative general senses from the facial region (head anterior to a coronal plane through the ears) are served via neurons of the trigeminal nerve, which enter the brainstem through the lateral midpons. Most fibers terminate in the principal sensory trigeminal nucleus. Other fibers bifurcate into collaterals, which branch and terminate in the principal sensory trigeminal nucleus and/or descend for a short distance in the spinal tract of n.V (spinal trigeminal tract) and terminate in the pars oralis of the spinal nucleus of n.V (spinal trigeminal nucleus). The principal trigeminal nucleus is the cranial equivalent of the nuclei gracilis and cuneatus. In all of these nuclei are located the cell bodies of the second-order neurons of the discriminative general senses (*see* **Fig. 10.6**).

From cell bodies of neurons of the second order, located in the principal sensory trigeminal nucleus and rostral portion of the spinal trigeminal nucleus, axons decussate in the pontine tegmentum and ascend as the trigeminothalamic tract (anterior trigeminal tract) before terminating in the ventral posteromedial thalamic nucleus (*see* **Fig. 10.6**). Some axons of second-order neurons of the principal sensory trigeminal nucleus ascend *uncrossed* as the posterior trigeminothalamic tract (posterior trigeminal tract) to the same thalamic nucleus.

Axons of third-order neurons arising in the ventral posterior medial thalamic nucleus pass through the posterior limb of the internal capsule and corona radiata before terminating in the head area of the postcentral gyrus. Following processing within this gyrus, connections via association fibers are made with areas 5 and 7 of the parietal lobe (*see* **Fig. 10. 5** and Chap. 25).

This trigeminal pathway is structurally and functionally the same as the dorsal column–medial lemniscal pathway. (1) The axonal projections from sensory receptors to columns in the postcentral gyrus are similar. (2) These connections are maintained and sharpened by the same processing circuits. (3) The projections from the ventral posterior medial nucleus are similar to those of the ventral posterior lateral nucleus. The projection fibers terminate in areas 1, 2, 3a, and 3b of the postcentral gyrus. Subsequent connections with SII and areas 5 and 7 of the parietal lobe are equivalent.

PATHWAYS SERVING CRUDE (LIGHT) TOUCH AND MOVEMENT SENSATION

Pathway From the Body, Limbs, and Back of Head

Crude touch and movement sensation from the body and the back of the head (C2 dermatome) is conveyed from peripheral receptors via first-order neurons with cell bodies in the dorsal root ganglia of the peripheral nerves to the posterolateral tract of Lissauer where the fibers bifurcate (*see* **Fig. 7.6**). In addition to those that terminate at the level of entry, some

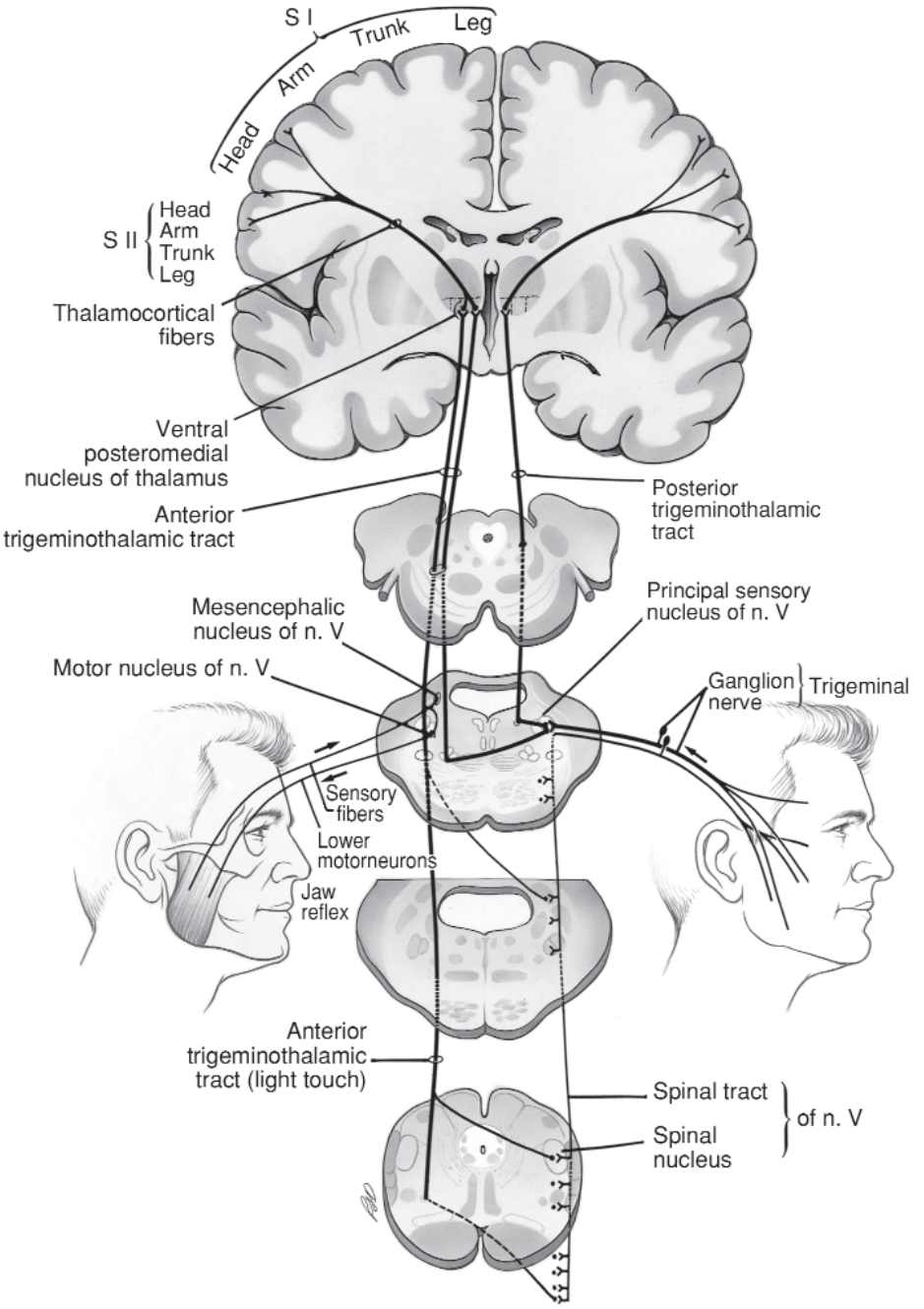


Figure 10.6: The discriminatory general sensory pathways originating in the brainstem are the anterior and posterior trigeminothalamic tracts. Note that the VPM thalamic nucleus projects to head regions of both SI and SII. The jaw reflex, illustrated on the left side of the figure, comprises (1) afferent fibers with cell bodies in the mesencephalic nucleus of n.V and (2) efferent (lower motoneurons) fibers with cell bodies in the motor nucleus of n.V. For details of structures in the brainstem, refer to Figs. 13.7, 13.10, 13.11, and 13.14.

ascend and descend several spinal levels before terminating on interneurons of the posterior horn. Processing occurs within the interneuronal circuits of the posterior horn.

The axons of neurons of the second order, with cell bodies presumably in laminae VI and VII, decussate through the anterior white commissure, ascend as the anterior spinothalamic tract which is somatotopically organized, and terminate in the ventral posterolateral nucleus of the thalamus. The anterior and lateral spinothalamic tracts together are referred to as the anterolateral tract or system (Chap. 9).

Third-order neurons in VPL emit axons that pass through the posterior limb of the internal capsule and the corona radiata before terminating in the postcentral gyrus. After neural processing in the gyrus, pyramidal neurons of the cortex project to the parietal association cortex. Crude touch is also conveyed via the posterior column–medial lemniscus pathway and the spinocervicothalamic pathway (*see* **Fig. 10.7**).

Pathways From the Facial Region

From receptors in the facial region (anterior to coronal plane through the ears), light touch fibers convey impulses via the three divisions of the trigeminal nerves (ophthalmic, maxillary, and mandibular) and to a small extent via cranial nerves VII, IX, and X. The cell bodies of first-order fibers are located in the trigeminal ganglion, geniculate ganglion, and superior ganglia of nerves IX and X. Upon entering the brainstem, some of these fibers terminate in the principal trigeminal nucleus and others descend in the spinal tract of n.V and terminate in the caudal part of the spinal trigeminal nucleus known as nucleus caudalis. Second-order neurons from these nuclei have axons that decussate and join the ascending trigeminothalamic tract and terminate in the ventral posteromedial nucleus of the thalamus. From this thalamic nucleus, axons pass through the internal capsule before terminating somatotopically as a homunculus in both the primary and secondary somatosensory cortex. In turn, SI and SII project to the parietal association cortex, where more processing occurs.

Lateral Cervical System (Spinocervicothalamic Pathway)

The lateral cervical system mediates touch, proprioception, vibratory sense, and to a small degree, noxious stimuli. This system is a fast-conducting four-neuron pathway (*see* **Fig. 10.7**).

The first-order neurons, with cell bodies in the dorsal root ganglia, have axons that terminate in laminae III, IV, and V of the dorsal horn. Second-order neurons from these laminae emit axons that ascend without decussating in the dorsolateral fasciculus of the lateral column to the lateral cervical nucleus (*see* **Fig. 7.6**). Third-order fibers from this nucleus, located in the upper two cervical spinal segments and the lower medulla, decussate in the lower medulla, ascend in the contralateral medial lemniscus, and terminate in the ventral posterior lateral nucleus of the thalamus. The fourth-order neurons project from VPL to the somatosensory cortex (SI and SII).

PROPRIOCEPTIVE PATHWAYS OF THE HEAD

Mesencephalic Nucleus of the Trigeminal Nerve; Jaw Jerk Reflex

Information from proprioceptive endings (e.g., muscle spindles) in the extraocular muscles and muscles of mastication and facial expression are conveyed to the CNS by Ia nerve fibers of cranial nerves III to VII. These Ia fibers have their cell bodies in the *mesencephalic nucleus of the trigeminal nerve*. This nucleus is unique, in that, it is the *only nucleus of primary sensory neurons located in the CNS* and is actually composed of *unipolar dorsal root (trigeminal) ganglion cell bodies* (*see* **Fig. 14.2**).

The jaw jerk is a two-neuron reflex, similar to the knee jerk reflex (*see* **Fig. 10.6**), which involves the temporalis, masseter, and internal pterygoid muscles. Tapping the chin of the slightly opened mouth with a reflex hammer evokes this reflex. The afferent limb of the

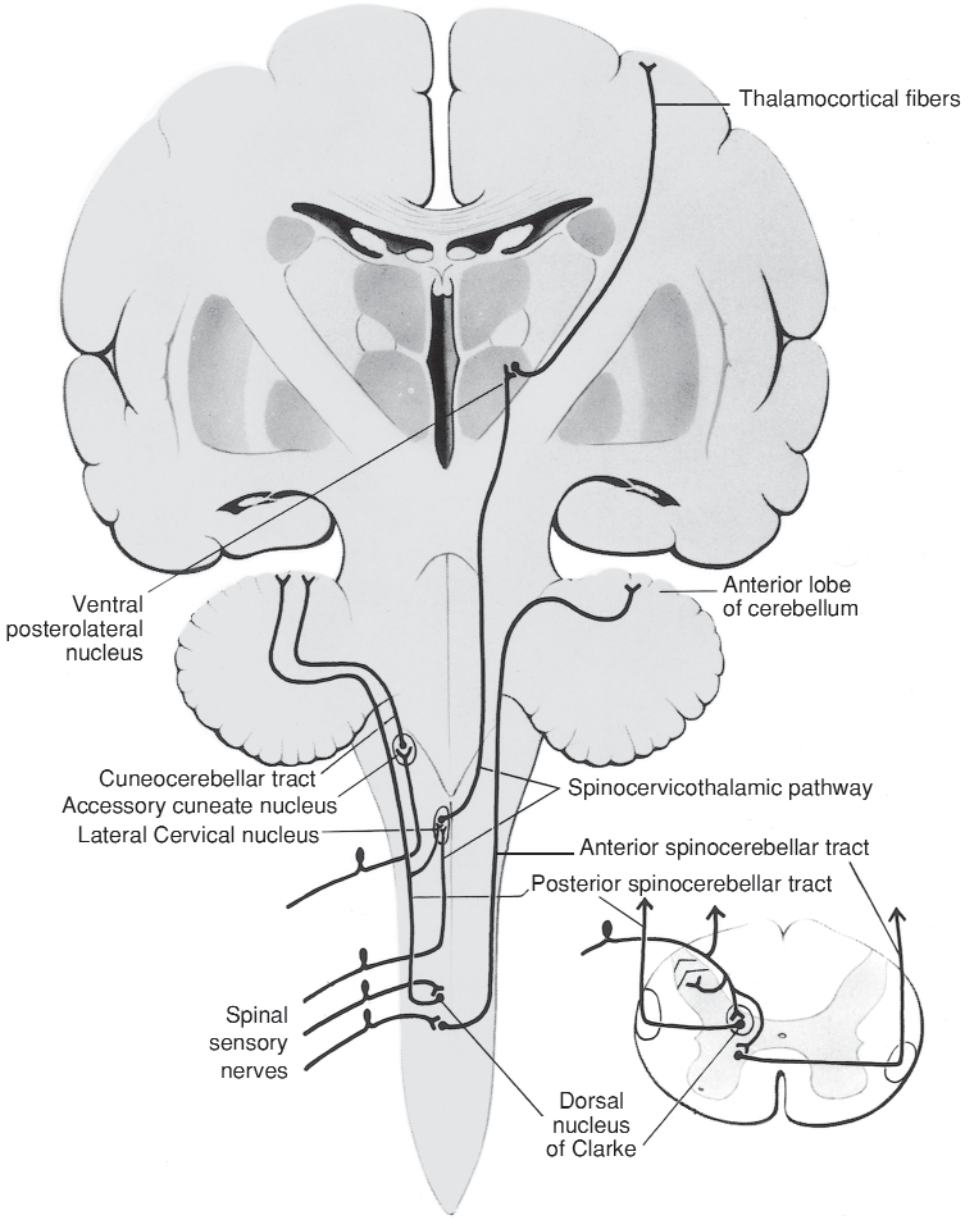


Figure 10.7: Ascending tracts from the spinal cord, including the anterior and posterior spinocerebellar tracts, cuneocerebellar tract, and spinocervicothalamic pathway.

reflex arc is composed of neurons with cell bodies of the mesencephalic nucleus. These neurons convey influences from the muscle spindles directly via collateral fibers to lower motoneurons in the motor nucleus of the trigeminal nerve. These lower motoneurons form the efferent limb innervating the muscles of mastication.

PROPRIOCEPTIVE PATHWAYS TO THE CEREBELLUM

The cerebellum plays an essential role in body movement and maintenance of equilibrium. Thanks to the cerebellum, voluntary muscles are coordinated in their contraction and relaxation so as to permit smooth movement. For this, the cerebellum requires a continuous supply of unconscious information from muscles, tendons, and joints to which receptors throughout the body and limbs contribute. The pathways for this input are outlined here (*see* **Fig. 10.7**); the main discussion of the cerebellum is in Chapter 17.

Information that arrives from muscle spindles (Ia fibers) and Golgi tendon organs (Ib fibers) is primarily unconscious and proprioceptive in nature, but, in addition, there are inputs from exteroceptors for crude touch, pressure, and pain. There are direct and indirect pathways from these receptors. The direct pathways convey input without an intervening synapse from the spinal neurons to the cerebellum. They are (1) the posterior spinocerebellar tracts for information from the lower limbs and lower half of the body and (2) the cuneocerebellar tracts for information from the upper limbs and upper half of the body (*see* **Fig. 10.7**). The indirect pathways are (1) the spinocervicocerebellar pathway, with a synaptic relay in the lateral reticular nucleus of the medulla (*see* **Fig. 13.9**), and (2) the spinoolivocerebellar pathway, with a synaptic relay in the inferior olivary nucleus of the medulla (*see* **Fig. 13.10**).

Two complete somatotopic representations can be traced on the cerebellar cortex, one homunculus on the anterior lobe and the other (in halves) on the posterior lobe (*see* **Fig. 18.2**).

Posterior Spinocerebellar Tract

First-order neurons that convey impulses from peripheral receptors into the spinal cord terminate in the dorsal nucleus (Clarke's nucleus), found in lamina VII. Second-order fibers arise from this nucleus, located at levels T1 through L2, and ascend uncrossed as the posterior spinocerebellar tract. The fibers enter the cerebellum by way of the inferior cerebellar peduncle, one of three fiber bundles on each side giving access to the cerebellum. The posterior spinocerebellar tract is primarily concerned with conveying information from muscles and joints in the lower limbs.

Cuneocerebellar Tract

First-order neurons ascend in the ipsilateral fasciculus cuneatus of the spinal cord and terminate in the accessory cuneate nucleus (equivalent to the dorsal nucleus of Clarke), which is located lateral to the cuneate nucleus (*see* **Fig. 13.9**). Second-order fibers, identified now as the cuneocerebellar tract, enter the cerebellum through the inferior cerebellar peduncle and terminate in portions of the anterior and posterior lobes dedicated to the upper extremities. This pathway is the rostral equivalent of the posterior spinocerebellar tract.

Anterior Spinocerebellar Tract (*see* Fig. 10.7)

This tract originates from cells, called *spinal border cells*, in the lumbosacral cord on the periphery of the anterior horn and other cells in the posterior horn and intermediate gray. Second-order fibers decussate in the spinal cord and ascend through the brainstem as the anterior spinocerebellar tract, which enters the cerebellum along the dorsal margin of the superior cerebellar peduncle. Most fibers terminate somatotopically in the vermis of the anterior lobe on the contralateral side in that part of the homuncular area representing the lower extremity and trunk. Some recross within the cerebellum to terminate on the same side as origin, whereas others terminate bilaterally (*see* **Fig. 18.2**).

Rostrospinocerebellar Tract

This tract is presumed to arise from cells in the intermediate gray zone of the cervical enlargement. It ascends as an uncrossed tract whose fibers pass through both the inferior and superior cerebellar peduncles before terminating in the area of the homunculus representing

the upper extremity in the anterior lobe of the cerebellum.

The pattern of termination of the posterior spinocerebellar and cuneocerebellar inputs to the cerebellum is somatotopic to form separate homunculi rostrally in the anterior lobe and caudally in the posterior lobe (*see* **Fig. 18.2**). The anterior spinocerebellar and rostrospinocerebellar tracts were previously thought to convey somatic sensory information from the lower and upper limbs, respectively. It is now thought that they relay *feedback signals* to the cerebellum, monitoring the amount and quality of activity in the descending motor pathways, rather than conveying information from the periphery (Chap. 17).

Indirect Pathways

The spinoreticular fibers of the anterolateral pathway include a population originating at all spinal levels and terminating in the lateral cervical nucleus and other small nuclei in the medulla. This *spinocervicocerebellar pathway* is completed by neurons arising from these nuclei and terminating in the cerebellum. In this way, the cerebellum receives exteroceptive input.

The s*pinoolivary tract,* activated by cutaneous and proprioceptive afferent fibers of the spinal nerves, originates from cell bodies located at all spinal levels (*see* **Fig. 7.6**). The tract terminates in the inferior olivary nuclei of the medulla (*see* **Fig. 13.10**). O*livocerebellar* fibers cross the midline and enter the cerebellum through the inferior cerebellar peduncle.

FUNCTIONAL CORRELATIONS

The general sensory pathways conveying pain and temperature, tactile sensibility, and discriminative senses have, with a few exceptions, similar features. The neurons of the first-order innervate receptors in the periphery and terminate within nuclei (or laminae) in the ipsilateral half of the spinal cord or brainstem. The cell bodies of these neurons are located in ganglia (with no synapses within them) just outside the CNS: dorsal root ganglia, trigeminal ganglion, geniculate ganglion, and superior ganglia of cranial nerves IX and X. The neurons of the second order have cell bodies in a nucleus on the ipsilateral side and give rise to axons that decussate to the contralateral side and ascend as tracts, which terminate in the thalamus (ventral posterior nucleus and posterior thalamic region). The neurons of the third order project from the thalamus to the postcentral gyrus (primary somatic area) and adjacent to the secondary somatic area (*see* **Fig. 25.3**). Note that the spinothalamic fibers (neurons of the second order) decussate at all levels of the spinal cord, with each fiber crossing at a spinal level near the location of its cell body, whereas all second-order neurons of the posterior column–medial lemniscal pathway have axons that decussate at a common level in the lower medulla, where they are known as internal arcuate fibers.

Crude touch can be conveyed via two pathways: (1) the anterior spinothalamic tract (and its cranial equivalent, the anterior trigeminal tract) and (2) the posterior column–medial lemniscal pathway (and its cranial equivalent, the anterior and posterior trigeminal tracts).

Loss of tactile sensibility is known as *tactile anesthesia*. Diminution is *tactile hypesthesia* and an exaggeration, which is often unpleasant, is *tactile hyperesthesia*. The latter can be accompanied by *paresthesias, the* sensations of numbness, tingling, prickling, and feeling of discomfiture.

Impairment of the Posterior Column-Medial Lemniscus Pathway

Interruption of the posterior column-medial lemniscus pathway causes disturbances in the appreciation of certain sensations and in the regulation and control of movements.

The alterations in the appreciation of the discriminative general senses include the following:

1. Diminution, not loss, of *crude touch*. This modality is partially retained because the

anterior spinothalamic tract is intact and functional.

2. Loss of *vibratory sense*. The perception of the "buzz" of vibrations is tested by placing the base of a vibrating tuning fork on a joint or bone (e.g., knee, elbow, finger, spinous process of vertebra).
3. *Astereognosis* (literally meaning not knowing solids) refers to loss of the ability to recognize a common object by feel and palpation. For example, a patient with astereognosis is unable to identify a key, coin, or pencil by handling or touch. The ability to recognize objects by sight is unimpaired.
4. Loss of *two-point discrimination* refers to the ability to recognize two blunt points as two points when applied simultaneously.
5. Loss of *position sense* refers to the ability to know where a part of the body is located or to appreciate movement of a joint.

Ataxia (without order) refers to unsteady, awkward, and poorly coordinated movements. It can be caused by lesions in the pathways for proprioceptive stimuli (i.e., the posterior column–medial lemniscus pathway including the dorsal roots, posterior column [posterior column ataxia], nuclei gracilis and cuneatus, and medial lemniscus. Patients show an unsteady gait while walking or turning; to reduce the unsteadiness, they walk with a broad base. In severe cases, a patient might stagger and fall while the eyes are closed. The signs of ataxia are more pronounced in the dark or with eyes closed. The severity of the symptoms is reduced when the subject can use visual cues; this is consistent with the concept that two or three of the following sources of sensory input are essential for adequate regulation of posture and movement: proprioceptive general senses, vision, and vestibular sense. *Romberg's sign* is often used to detect posterior column ataxia. In the erect position with feet close together, an ataxic patient will sway when the eyes are closed; swaying is reduced or abolished when the eyes are opened. *Cerebellar ataxia* is another form of this disorder (Chap. 17).

Spinal Cord Lesions and the Crude (Light) Touch Pathways

Following a lesion in the spinal cord, the appreciation of light touch is less apt to be impaired than any of the other sensory modalities. This is because light touch is conveyed by more than one route: the posterior columns, the anterolateral pathway, and the lateral cervical pathway. A unilateral lesion of the posterior columns results in the loss of two-point discrimination on the same side of the body as the lesion while light touch persists, although it might be marginally lowered, because the anterolateral pathway is intact. A unilateral lesion of the anterolateral pathway results in loss of pain perception on the opposite side of body, but, again, light touch persists or might be marginally lowered because the posterior columns are intact.

SUGGESTED READINGS

Brown AG. The spinocervical tract. *Prog. Neurobiol.* 1981;17:59–96.

Burgess PR, Wei JY, Clark FJ, Simon J. Signaling of kinesthetic information by peripheral sensory receptors. *Annu. Rev. Neurosci.* 1982;5:171–187.

Carpenter MB, Sutin J. *Human Neuroanatomy.* Baltimore: Williams & Wilkins; 1983.

Cascio CJ, Sathian K. Temporal cues contribute to tactile perception of roughness. *J. Neurosci.* 2001;21:5289–5296.

Connor CE, Johnson KO. Neural coding of tactile texture: comparison of spatial and temporal mechanisms for roughness perception. *J. Neurosci.* 1992;12:3414–3426.

Cormack DH. *Ham's Histology.* Philadelphia: Lippincott Williams & Wilkins; 1987.

Craig AD, Dostrovsky JO. Medulla to thalamus. In Wall PD, Melzack R, eds. *Textbook of pain.* New York: Churchill Livingston; 999:183–214.

Darian-Smith I. Touch in primates. *Annu. Rev. Psychol.* 1982;33:155–194.

Field T. *Touch.* Cambridge, MA: MIT Press, 2001.

Garcia-Anoveros J, Corey DP. The molecules of mechanosensation. *Annu. Rev. Neurosci.* 1997; 20:567–594.

Goodwin AW, Wheat HE. How is tactile information affected by parameters of the population such as

non-uniform fiber sensitivity, innervation geometry and response variability? *Behav. Brain Res.* 2002;135:5–10.

Goodwin AW, Wheat HE. Sensory signals in neural populations underlying tactile perception and manipulation. *Ann. Rev. Neurosci.* 2004;27:53–77.

Goodwin AW, Macefield VG, Bisley JW. Encoding of object curvature by tactile afferents from human fingers. *J. Neurophysiol.* 1997;78:2881–2888.

Hudspeth AJ, Logothetis NK. Sensory systems. *Curr. Opin. Neurobiol.* 2000;10:631–641.

Iggo A. Sensory receptors in the skin of mammals and their sensory functions. *Rev. Neurol. (Paris)* 1985;141:599–613.

Iggo A, Andres KH. Morphology of cutaneous receptors. *Annu. Rev. Neurosci.* 1982;5:1–31.

Iwamura Y, Iriki A, Tanaka M. Bilateral hand representation in the postcentral somatosensory cortex. *Nature.* 1994;369:554–556.

Jenmalm P, Birznieks I, Goodwin AW, Johansson RS. Influence of object shape on responses of human tactile afferents under conditions characteristic of manipulation. *Eur. J. Neurosci.* 2003; 18:164–176.

John KT, Goodwin AW, Darian-Smith I. Tactile discrimination of thickness. *Exp. Brain. Res.* 1989; 78:62–68.

Johnson KO. The roles and functions of cutaneous mechanoreceptors. *Curr. Opin. Neurobiol.* 2001; 11:455–461.

Lindsay RM. Role of neurotrophins and trk receptors in the development and maintenance of sensory neurons: an overview. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 1996;351: 365–373.

Mountcastle VB. The columnar organization of the neocortex. *Brain* 1997;120(Pt. 4):701–722.

Pare M, Elde R, Mazurkiewicz JE, Smith AM, Rice FL. The Meissner corpuscle revised: a multiafferented mechanoreceptor with nociceptor immunochemical properties. *J. Neurosci.* 2001;21:7236–7246.

Schmidt RF, ed. *Fundamentals of Sensory Physiology.* New York: Springer-Verlag; 1986.

Sinclair DC. *Mechanisms of Cutaneous Sensation.* New York: Oxford University Press; 1981.

Vallbo AB, Olausson H, Wessberg J, Kakuda N. Receptive field characteristics of tactile units with myelinated afferents in hairy skin of human subjects. *J. Physiol.* 1995;483 (Pt. 3): 783–795.

Wessberg J, Olausson H, Fernstrom KW, Vallbo AB. Receptive field properties of unmyelinated tactile afferents in the human skin. *J. Neurophysiol.* 2003;89:1567–1575.

Wheat HE, Goodwin AW, Browning AS. Tactile resolution: peripheral neural mechanisms underlying the human capacity to determine positions of objects contacting the fingerpad. *J. Neurosci.* 1995;15:5582–5595.

11
Motoneurons and Motor Pathways

Lower Motor Neurons
Upper Motor Neurons
Motor Areas of the Cerebral Cortex
Motor Pathways
Voluntary Movements

The sensory systems create our mental images of the external world. These representations provide us with information and cues that guide the motor systems to generate movements produced by the coordinated contractions and relaxations. The motor systems are hierarchically organized in the central nervous system (CNS) as the spinal neuronal circuits that control the automatic stereotypic reflexes (Chap. 8). Higher centers in the brainstem mediate postural controlled and rhythmic locomotor movements. The highest centers, including the motor areas of the cerebral cortex, initiate and regulate complex skilled voluntary movements.

The major components of the somatic motor system are organized and longitudinally oriented along the neuraxis as two pathway systems: (1) the *phylogenetically new direct pathways* that fine-tune and control voluntary movements namely the corticospinal tract and the corticobulbar tract originating in the cerebral cortex and project to terminate in the anterior horn of the spinal cord and nuclei of the brainstem; (2) the *phylogenetically old more diffuse and indirect pathways* that primarily mediate reflex and postural control of the musculature, namely descending indirect pathways from the cerebral cortex to brainstem nuclei that project to the anterior horn of the spinal cord (e.g., corticoreticular and cortico preticospinal tracts).

Two prominent neural structures related to these major components of the motor system are the *cerebellum* (Chap. 18) and the four principal nuclei of the *basal ganglia* (striatum, globus pallidus, substantia nigra, and subthalamic nucleus; Chap. 24). Both are integral neural structures involved in *parallel re-entrant circuit systems*. Both the cerebellum and basal ganglia receive direct or indirect input from the cerebral cortex and, following processing, project influences to discrete nuclei of the thalamus that relay (re-entry) via the thalamocortical circuit to the cerebral cortex. Their outputs are also conveyed to the brainstem and, subsequently, to the spinal cord (Chaps. 3 and 24). Each re-entrant circuit includes both direct and indirect pathways that facilitate and inhibit movement. The *cerebellum* is involved in modulating motor systems, coordinating eye movements, balance, body and limb movements, motor learning, and even some cognitive functions. The *basal ganglia* have major roles in the control of voluntary movements and, to some degree, with cognition and nonmotor behavior.

LOWER MOTOR NEURONS

The voluntary (striated, skeletal) muscles are innervated by alpha motoneurons, which have heavily myelinated, fast-conducting axons that terminate in motor end plates of extrafusal striated muscle fibers. Because these neurons are the only pathway through which the sensory systems and the descending upper motoneuron pathways of the CNS exert their influences

upon striated muscles, they function as the *final common pathway*, the final link between the CNS and the voluntary muscles. The intrafusal striated muscles of the muscle spindles are innervated by gamma motoneurons, which have lightly myelinated, slow-conducting axons.

The term *lower motoneuron*, as used in clinical neurology, refers to motor neurons that innervate the voluntary muscles. Destruction of the lower motoneurons results in abolishing voluntary and reflex responses, rapid atrophy, and flaccid paralysis of the muscles innervated; these signs are referred to as a lower motoneuron paralysis (Chap. 12). The lower motoneurons have their cell bodies within the anterior horn of the spinal cord and in the motor nuclei of the brainstem; the latter innervate voluntary muscles supplied by the cranial nerves (e.g., muscles of facial expression) (*see* **Figs. 8.1 and 8.2**).

The term *upper motoneuron* refers to descending motor pathways within the CNS that either directly or indirectly exerts influences on lower motoneurons. The activities of alpha and gamma motoneurons are affected by inputs from peripheral receptors via the spinal and cranial nerves and from upper motoneurons. At spinal cord levels, local interneurons, part of intrasegmental and intersegmental circuits within the gray matter, exert both excitatory and inhibitory influences on these lower motoneurons.

Alpha and Gamma Motorneurons Compared

Several differences exist between alpha and gamma motoneurons:

1. Alpha motoneurons can be stimulated monosynaptically (i.e., directly, not through interneurons) by groups Ia and II afferent fibers from muscle spindles and by some terminals of the corticospinal, lateral vestibulospinal and medullary reticulospinal tracts. Gamma motoneurons are not stimulated monosynaptically.
2. Alpha motoneurons emit axon collaterals that terminate on Renshaw cells, which in turn, have inhibitory synapses with the same alpha motoneurons. This forms a negative feedback circuit that serves to turn off an active alpha motoneuron so that it can be excited again (*see* **Fig. 3.11**). Gamma motoneurons are not linked to Renshaw cells.

The *lower motoneurons* are the general somatic efferent (GSE) components of spinal nerves and of cranial nerves III, IV, VI, and XII, which innervate the extraocular and tongue musculature. They are also special visceral efferent (SVE) components of cranial (branchiomeric) nerves V, VII, IX, X, and XI, which innervate the muscles of mastication and facial expression as well as the pharyngeal and laryngeal musculature (Chap. 14).

Lower motoneurons of the spinal cord are often called *anterior horn motoneurons* because of the position of their cell bodies. It is important to recognize that lower motoneuron axons are in both cranial and spinal nerves. As indicated in Chapter 7, an alpha motoneuron and all the muscle fibers it innervates is called a *motor unit*.

Location of Cell Bodies of Lower Motoneurons

The cell bodies of the alpha and gamma motoneurons are organized into functionally defined groups in lamina IX of the ventral horn and into general somatic cranial motor nuclei in the brainstem (Chap. 14). The dendrites of these neurons extend beyond the designated borders of lamina IX.

1. Motoneurons are arranged in a medial–lateral topographic pattern in the anterior horn (*see* **Fig. 11.1**). The medial group comprises motoneurons that innervate axial muscles (neck and back). An intermediate group innervates proximal muscles of the limbs (shoulder and arm, hip and thigh). The most lateral group consists of neurons that innervate the distal muscles of limbs (forearm and hand, leg and foot).
2. The motoneurons follow a flexor–extensor pattern (*see* **Fig. 11.1**). The flexor muscle group is located dorsally and the extensor muscle group is located ventrally in the anterior horn.

3. The motoneurons innervating a specific muscle or related muscles are clustered in a narrow, longitudinally oriented, three-dimensional column. This column extends through more than one spinal segment. As a consequence, each muscle is innervated by axons originating from more than one spinal segment. Thus, a lesion limited to one spinal root or nerve will result in only a partial paralysis (paresis) of the muscles involved.
4. The alpha motoneurons are presumed to be organized into groups on the basis of their functional attributes as (1) phasic motoneurons and (2) tonic motoneurons. The phasic

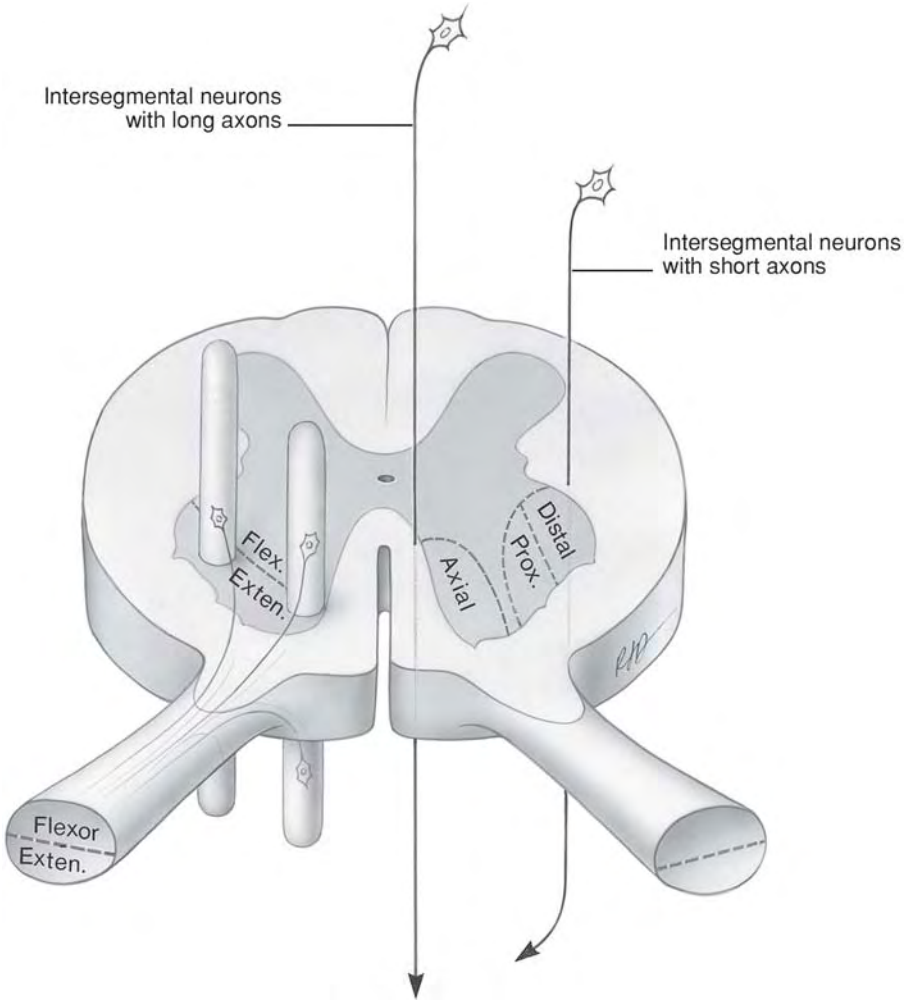


Figure 11.1: The alpha and gamma motoneurons are arranged in functionally defined groups in lamina IX of the ventral horn. The motoneurons located medially innervate axial (neck and back) musculature and those located laterally innervate the proximal and distal limb musculature. The motoneurons located dorsally innervate flexor muscles and those located ventrally innervate extensor muscles. The medial motoneurons are interconnected by intersegmental neurons with long axons, and the lateral motoneurons are interconnected by intersegmental neurons with shorter axons. The cylinder extending through more than one spinal segment in lamina IX represents the distribution of lower motoneurons innervating a specific muscle or related muscles.

motoneurons are large and fire with brief bursts at high frequencies. They are active during rapid movements of short duration that exert great force. The tonic motoneurons are relatively small and fire with brief bursts at low frequencies. They are active during delicate movements requiring little force and that sustain moderate tension for an extended period of time.

5. The *intersegmental interneurons* (*propriospinal interneurons*, Chap. 6) coordinating alpha and gamma motoneurons at different spinal cord segments have axons located in the white matter (*see* **Fig. 11.1**). The medial motoneurons (axial muscles) are interconnected by intersegmental neurons with long axons. The latter extend through many spinal levels in the anterior funiculus. The lateral motoneurons (limb muscles) are interconnected by intersegmental neurons with shorter axons. The latter extend through a lesser number of spinal segments in the lateral funiculus.

UPPER MOTOR NEURONS

Upper motoneuron pathways convey facilitatory (excitatory) and inhibitory signals to control lower motoneuron activity. These descending pathways are regulated directly or indirectly by the cerebral cortex, cerebellum, and basal ganglia (Chaps. 24 and 25). In turn, the upper motoneurons synapse directly, and indirectly through interneurons, with the alpha and gamma motoneurons that integrate coordinated skeletal muscle reflexes and voluntary movements.

The *descending upper motoneuron pathways, located exclusively within the CNS*; comprise the *corticospinal (pyramidal)* and *corticobulbar tracts* originating in the cerebral cortex (*see* **Figs. 11.2 and 11.3**), the *rubrospinal* and *tectospinal tracts*, originating in the midbrain (*see* **Fig. 11.3**), and the *reticulospinal* and *vestibulospinal tracts*, originating in the lower brainstem (pons and medulla) (*see* **Figs. 11.3 and 16.9**).

Clinicians often equate the term *upper motoneuron paralysis* with injury to the *lateral corticospinal tract,* sometimes including the *corticobulbar tract* (cortical fibers that terminate in the brainstem). In addition, the corticospinal tract is referred to as the *pyramidal tract* because its fibers go through the medullary pyramid. The term *extrapyramidal system* refers to all other descending motor tracts, which do not go through the pyramid, and their processing centers.

Upper motoneurons have significant roles in voluntary motor activity, maintenance of posture and equilibrium, control of muscle tone, and reflex activity. In general, the influences conveyed via the descending supraspinal pathways exert their effects (1) on groups of muscles and movements (e.g., flexion, extension, adduction) not primarily on one specific muscle, and (2) reciprocally upon agonist and antagonist muscle groups (e.g., they facilitate flexion and inhibit extension, or inhibit flexion and facilitate extension). The upper motoneurons exert their influences on lower motoneurons through both direct monosynaptic connections and via indirect multisynaptic connections with interneurons.

MOTOR AREAS OF THE CEREBRAL CORTEX

Several areas of the cerebral cortex are designated as motor areas. These include the *primary motor cortex* (area 4, motor strip, MI), *premotor cortex* (areas 6 and 8), *supplementary motor cortex* (portion of area 6), and *secondary motor cortex* (MII) (*see* **Figs. 25.3 and 25.4**).

The *primary motor cortex* (area 4) is located in the precentral gyrus and the rostral half of the paracentral lobule. Direct electrical stimulation of this area evokes movements associated with the voluntary muscles on the contralateral side. A map of this electrically excitable cortex produces a somatotopically organized *motor homunculus* (little man; *see* **Fig. 25.4**). The homunculus hangs upside down with the larynx and tongue in the lowest part adjacent to

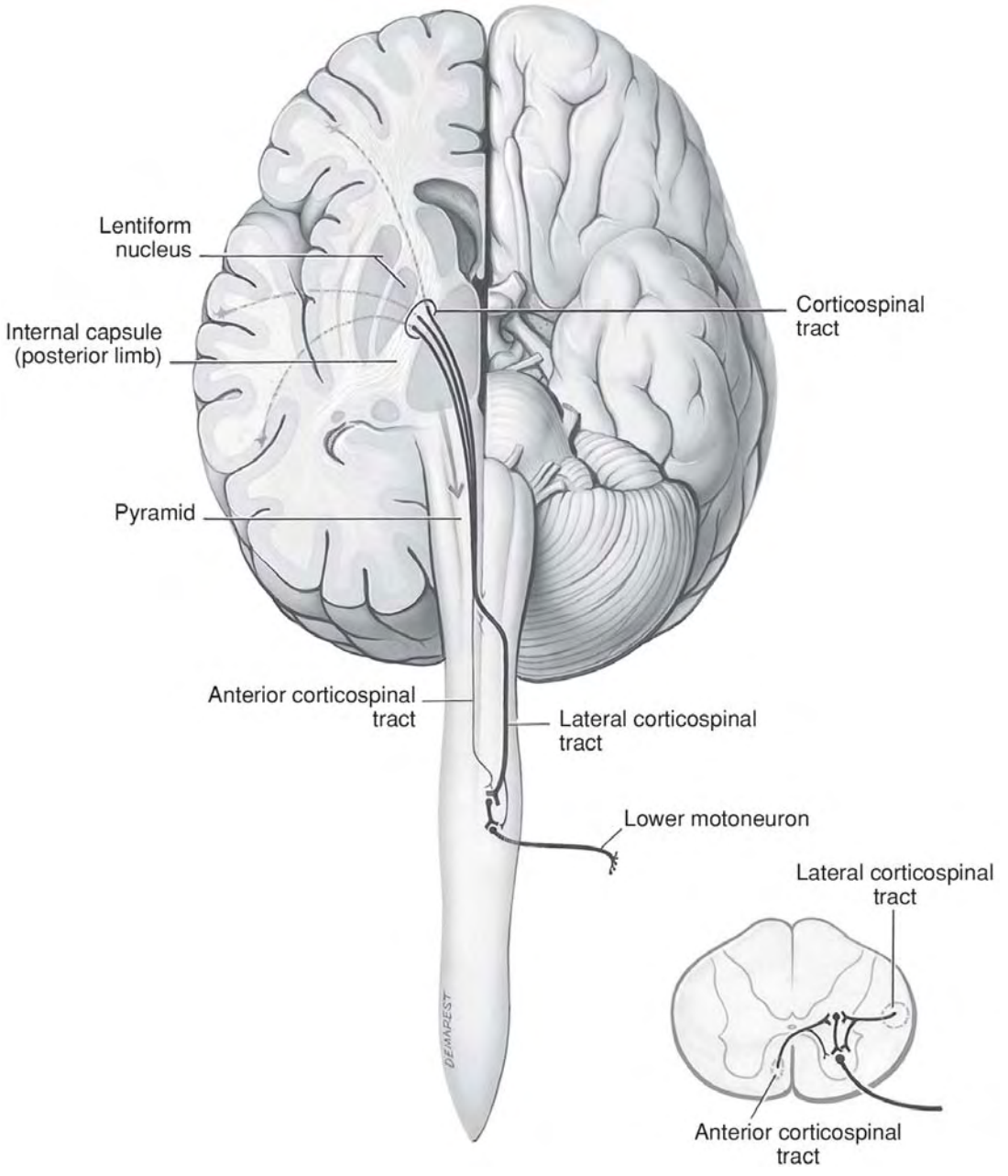


Figure 11.2: Corticospinal pathways. These pathways are composed of descending fibers that originate from widespread areas of the cerebral cortex and pass through the posterior limb of the internal capsule, crus cerebri, pons, pyramid, and spinal cord. Most fibers terminate upon spinal interneurons that, in turn, synapse with lower motoneurons. Some fibers terminate directly upon lower motoneurons. The lateral corticospinal tract crosses over at the lower end of the medulla as the pyramidal decussation, and the anterior corticospinal tract crosses over in upper spinal cord levels. A small number of lateral corticospinal tract fibers do not decussate (not illustrated).

the lateral fissure, followed upward by the head, upper limb, thorax, abdomen, and lower extremity; the latter is located in the rostral paracentral gyrus. The amount of motor cortex devoted to specific regions is roughly proportional to the skill, precision, and control of the movements in that region (e.g., large area for larynx, tongue, thumb, and lips). The role of area 4 is to participate in the execution of skilled and agile voluntary movements.

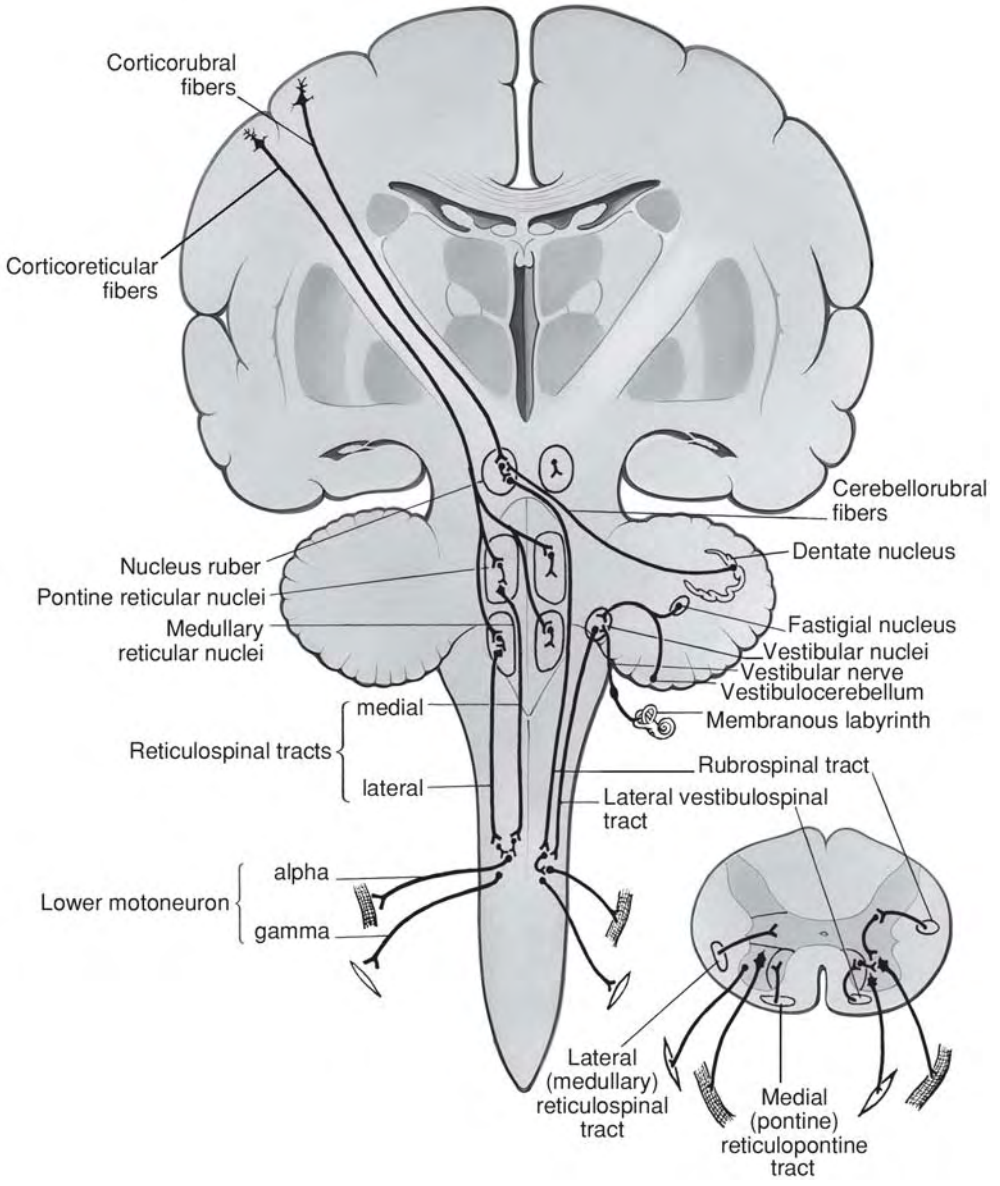


Figure 11.3: Descending motor pathways to the spinal cord including the reticulospinal tracts (corticoreticulospinal pathways), rubrospinal tracts (corticorubrospinal pathways), and vestibulospinal tracts. The corticoreticular fibers terminate bilaterally but with a slight contralateral preponderance.

Although the motor cortex contributes to the regulation of axial and proximal limb musculature, it has a more critical role in the control of the distal muscles on the contralateral side of the body.

The *premotor cortex*, located rostral to area 4, consists of areas 6 and 8. Area 8, known as the *frontal eye field*, is concerned with eye movements. Stimulation of this area results in conjugate movements of the eyes directed to the opposite side. The *premotor cortex* on the lateral surface of the lobe has (1) a primary role in the control of the proximal limb and axial musculature and (2) an essential role in the initial phases of orientation movements of the body and upper limbs directed toward a target. The *supplementary motor cortex*, located on the medial aspect of area 6, has a somatotopic organization. It is important for programming of patterns and sequences of movements. For example, the response to electric stimulation on one side of this area activates complex patterns of movement not only of the contralateral limbs but also includes bilateral movements of the limbs of both sides. Both the premotor cortex and the supplementary motor cortex project to the primary motor cortex.

General Statement

The primary motor cortex (area 4), premotor cortex, and supplementary motor cortex are somatotopically organized. Area 4 and the supplementary motor cortex have direct projections via the corticospinal tracts to the spinal cord. The premotor cortex projects primarily to the reticular formation of the pons and medulla. The premotor cortex and the supplementary motor cortex are higher ordered motor cortical regions that have connections with the primary motor cortex.

MOTOR PATHWAYS

The descending motor pathways are subdivided into systems called the (1) corticospinal and corticobulbar tracts, (2) corticoreticulospinal pathways, (3) corticorubrospinal pathway, (4) corticotectospinal pathway, (5) vestibulospinal tracts, and (6) raphe–spinal and ceruleus–spinal pathways (aminergic pathways). These pathways are involved with motor circuits associated with the spinal cord and spinal nerves. These systems also have equivalent roles influencing local motor circuits of the brainstem and the cranial nerves. Many of the fibers of the systems have significant roles in feedback circuits that modulate the activities of the ascending sensory pathways (Chaps. 9 and 10).

Corticospinal Tract

The fibers of the corticospinal tract (CST) originate from pyramidal cells (cell bodies with pyramid shape) in the cerebral cortex and terminate in the spinal cord. About one-third of the fibers originate from Brodmann's area 4, one-third from area 6 of the frontal lobe, and the remainder from areas 3, 1, 2, and 5 of the parietal lobe. Most fibers terminate on interneurons of spinal cord circuits that synapse on the lower motoneurons. About 3% of CST axons originate from giant pyramidal cells in area 4, called Betz cells; these axons have monosynaptic contacts with some alpha motoneurons and interneurons in lamina IX.

The axons of the somatotopically organized corticospinal tract descend through the ipsilateral posterior limb of the internal capsule (near the genu), the middle portion of the crus cerebri of the midbrain, the basilar pons and the pyramids of the medulla (*see* **Figs. 1.8, 11.2, 13.4, and 13.5**). The CST emits collateral branches to some nuclei of the basal ganglia, thalamic nuclei, the red nucleus, and brainstem reticular nuclei, thereby exerting widespread influences on nuclei within the brain as well as on lower motoneurons.

At the junction between the medulla and spinal cord, approximately 90% of the 1 million fibers in each tract cross as the pyramidal decussation and descend in the posterior half of the lateral funiculus as the *lateral corticospinal tract*, which terminates at all spinal levels in laminae IV through VII and IX (*see* **Fig. 7.5**). About 10% of the fibers descend without crossing in the ipsilateral anterior funiculus as the

anterior corticospinal tract (CST), which terminates after crossing in the anterior white commissure in lamina VIII in cervical and upper thoracic cord levels. A small proportion of fibers, roughly 2%, descend without decussating as the uncrossed lateral corticospinal tract.

The functional roles of these pathways can be summarized as follows: (1) The lateral CST is preferentially involved with movements of the distal upper and lower extremities (hands and feet) and, thus, has a key role in the execution of skilled movements; (2) the anterior CST is preferentially involved with control of axial muscles (neck, shoulder, and trunk); and (3) those lateral CST fibers originating from the parietal lobe form a reflected feedback pathway modulating sensory input in the dorsal horn of the spinal cord (Chap. 9).

The CST exert their influences on local spinal reflex circuits involving interneurons and both alpha and gamma motoneurons. Glutamate is the likely neurotransmitter released by these tracts (Chap. 15). Acting through interneurons (any neuron that is intermediary in position between two neurons), the CST generally evokes excitatory postsynaptic potentials [EPSPs] on the local circuits involved with the flexor limb musculature (agonists) and IPSPs on the circuits involved with the extensor musculature (antagonists).

Corticobulbar Tract

The cerebral cortical (supranuclear, upper motoneuron) projections to the nuclei of the cranial nerves and brainstem nuclei of the ascending pathways are known as *corticobulbar fibers*. This pathway has a role similar to that of the CST:

1. *Indirect corticobulbar fibers* (often included with corticoreticular fibers) originate in the premotor, motor, and somesthetic areas (areas 6, 4, 3, 1, 2, and 5) of the cerebral cortex, descend in the genu of the internal capsule, and pass through both the ipsilateral and contralateral brainstem before synapsing directly with interneurons of the brainstem reticular formation (see *pseudobulbar palsy* in Chap. 17). These interneurons are integrated in circuits, which innervate the cranial nerve motor nuclei, including nerves III, IV, V, VI, VII, and XII and the nucleus ambiguus. The descending influences to the nucleus of the accessory nerve are probably conveyed via uncrossed indirect corticobulbar projects, which facilitate the contraction of the ipsilateral sternocleidomastoid and trapezius muscles.
2. *Direct corticobulbar fibers* from each hemisphere to the motor nuclei of the cranial nerves originate in the cerebral cortex, descend in the genu of the internal capsule, and pass as crossed and uncrossed fibers to and through both the ipsilateral and contralateral brainstem before synapsing with the lower motoneurons of the motor nuclei of cranial nerves V (muscles of mastication), VII (muscles of facial expression), and XII (tongue musculature. The lower motoneurons innervating the muscles of facial expression below the level of the eye (e.g., buccinator, labial muscles) are a clinically significant exception (Chap. 14); they are innervated only by corticobulbar fibers, which have decussated, not by descending uncrossed fibers.
3. Fibers of reflected feedback pathways project influences from sensory cortical areas 3, 1, 2, and 5 (parietal lobe) to sensory relay nuclei of the ascending pathways, including the nuclei gracilis and cuneatus of the posterior column–medial lemniscal pathway, principal sensory trigeminal nucleus, spinal trigeminal nucleus, and the nucleus of the solitary fasciculus. These fibers are involved with processing sensory influences in the nuclei of ascending pathways.

Extrapyramidal System

With the exception of the pyramidal system, the descending supraspinal tracts, together with their nuclei and feedback circuits, influencing somatic motor activity of voluntary muscles, are incorporated into the so-called "extrapyramidal system." The term is loosely used and many authorities have discarded it. The descending tracts, which convey influences to the lower motoneurons, are actually

neuronal links in pathway systems of complex circuitry involving the cerebral cortex, basal ganglia, thalamus, cerebellum, brainstem reticular formation, and related structures. Such systems include the corticorubrospinal, cerebellorubrospinal, corticoreticulospinal, cerebelloreticulospinal, cerebellovestibulospinal, and vestibular nerve–vestibulospinal pathways. The extrapyramidal system is discussed in Chapter 24.

Corticoreticulospinal: Corticoreticular and Reticulospinal Tracts

The sequence of corticoreticular and reticulospinal tracts comprises the *corticoreticulospinal pathway* (*see* **Fig. 11.3**). From their origin in the premotor cortex (area 6) of the frontal lobe, corticoreticular fibers descend along with the corticospinal tract and terminate in the pontine and medullary reticular nuclei of the brainstem reticular formation on both sides. The latter also receives input from ascending pathways and the cerebellum (Chap. 13).

The *reticulospinal tracts* include the *lateral (medullary) reticulospinal tract* and the *medial (pontine) reticulospinal tract* that extend throughout the spinal cord. These tracts are primarily uncrossed and are not somatotopically organized.

The *medial (pontine) reticulospinal tract* originates from the nuclei reticularis, pontis oralis, and caudalis (Chap. 13) and descends mainly as uncrossed fibers in the anterior funiculus (included in medial longitudinal fasciculus [MLF], *see* Medial Longitudinal Fasciculus) and terminates at all spinal levels in the medial parts of the ventral horn and intermediate zone in laminae VII and VIII (*see* **Figs. 7.5 and 7.6**)

The *lateral (medullary) reticulospinal tract* originates from the nucleus reticularis gigantocellularis (*see* **Fig. 13.10**) and descends mainly as uncrossed fibers in the anterior funiculus lateral to fibers of the MLF. The fibers terminate at all spinal levels on interneurons in the medial part of the ventral horn and intermediate zone in laminae VII and IX (*see* **Figs. 7.5 and 7.6**). The fibers of both reticulospinal tracts terminate on interneurons and some on gamma motoneurons (*see* **Fig. 11.3**). They can facilitate and inhibit local spinal circuits involved in both reflex and voluntary movements. These corticoreticulospinal pathways are involved in maintaining posture (upright position) for movements that orient the body toward the external stimuli and for crude stereotypic voluntary movements of the extremities, such as extending the limb toward an object.

This pathway acts as a link in the autonomic nervous system, conveying influences to the sympathetic and parasympathetic centers in the spinal cord (*see* **Fig. 11.3**). Descending fibers from the autonomic centers in the hypothalamus project their influences directly to spinal levels and to visceral centers in the reticular formation of the lower brainstem. This region, including the nucleus gigantocellularis, contains cardiovascular, respiratory, and other visceral centers. Their influences are conveyed to the spinal cord via the lateral reticulospinal tract. Expressions of this include the modulation of the heartbeat, dilatation of the pupil, perspiration, shivering, and the activity of sphincters of the gastrointestinal and urinary systems.

Corticorubrospinal Pathway: Corticorubral and Rubrospinal Tracts

The corticorubral tract originates in areas 4 and 6 and terminates in the ipsilateral nucleus ruber (red nucleus) of the midbrain (*see* **Figs. 11.3 and 13.16**). This nucleus is a processing center of the corticorubrospinal pathway. The rubrospinal tract originates in the magnocellular portion of the red nucleus and crosses over in the midbrain tegmentum as the ventral tegmental decussation. It descends in the lateral funiculus of the spinal cord and terminates in laminae V, VI, and VII at all spinal levels. This pathway facilitates the local circuitry and the alpha and gamma motoneurons involved with the flexor musculature and inhibits that involved with the extensor musculature, especially that of the upper extremity. In this respect, it is functionally similar to the lateral corticospinal tract.

Vestibulospinal Tracts

The lateral vestibular nucleus gives rise to the lateral vestibulospinal tract, which descends as an uncrossed somatotopically organized tract throughout the entire length of the spinal cord in the anterior funiculus (*see* **Figs. 11.3 and 16.9**). It terminates in the medial part of the anterior horn and intermediate zone and selectively excites motoneurons to the extensors. Fibers from the medial vestibular nucleus descend mainly, but not entirely, uncrossed as the medial vestibulospinal tract within the medial longitudinal fasciculus of the anterior funiculus (*see* **Fig. 16.9**). The vestibulospinal tracts terminate almost exclusively on interneurons of laminae VII and VIII, which, in turn, interact with the alpha and gamma motoneurons of lamina IX; some fibers terminate monosynaptically on alpha motoneurons in lamina IX. Both tracts exert facilitatory influences on muscle stretch (myotatic) reflexes. This reinforces the tonus of the extensor musculature of the trunk and extremities to maintain the upright posture.

Corticotectal, Tectobulbar, and Tectospinal Tracts

The corticotectal tract originates in visual association areas 18 and 19 and terminates in the superior colliculus and other nuclei in the midbrain tectum. The tectobulbar tract terminates in the paramedian pontine reticular formation (PPRF). The PPRF is involved with coordination of the conjugate movements of the eyes and their reflexive movements (Chaps. 14 and 16).

The tectospinal tract from the superior colliculus decussates as the dorsal tegmental decussation in the midbrain tegmentum to join and descend in the ventral funiculus of the spinal cord with the MLF. Its fibers terminate in laminae VII and VIII of cervical and upper thoracic levels. The corticotectospinal and corticotectobulbar pathways are involved with conveying influences via interneurons to lower motoneurons innervating the extraocular, neck, and back musculature. In addition, the vestibular system is integrated into the activities of these muscles. These systems of pathways account for turning movements of the head, eyes, and trunk in response to visual and vestibular inputs (Chaps. 18 and 19). The eye movements are essentially reflexive and not volitional. The influences from visual area 19 are associated with pursuit movements of the eyes (Chap. 19). In essence, these pathways coordinate eye movements involving the axial (trunk) muscles as well as the vestibular influences on the muscles of the extremities during balancing activities.

Medial Longitudinal Fasciculus

The *medial longitudinal fasciculus* (MLF) is a composite bundle of fibers located in the brainstem (Chap. 13) and spinal cord (*see* **Figs. 7. and 16.9**). It consists of a *descending component* and an *ascending component*. The descending component extends from the midbrain throughout the spinal cord. It comprises the medial vestibulospinal tract, the medial reticulospinal tract (both described earlier), and the tectospinal tract originating from the superior colliculus. The latter descends through the MLF as far as upper thoracic levels and terminates in laminae VII and VIII. The ascending component is the *vestibuloocular reflex pathway* in the pons and midbrain, extending from the level of the abducens nucleus to that of the oculomotor nuclei. This pathway originates from cell bodies located in the vestibular nuclei and in the paramedian pontine reticular formation (PPRF, Chap. 16). In addition, the MLF contains reciprocal fiber systems interconnecting the abducens and oculomotor nuclei (for conjugate eye movements) (Chaps. 14 and 16).

Raphe–Spinal and Locus Ceruleus–Spinal Pathways (Aminergic Pathways)

The monoamine transmitters they release characterize the projections from certain brainstem nuclei to the spinal cord, called aminergic pathways. Among these are serotonin (5-HT, 5-hydroxytryptamine) and norepinephrine (noradrenaline) (Chap. 15).

Serotonin is located in neurons of the nucleus raphe magnus, other raphe nuclei, and

some neurons of the brainstem reticular formation (Chaps. 13 and 15). Axons from these nuclei descend in the dorsolateral funiculus and terminate in laminae I, II, and V and on the preganglionic sympathetic neurons of lamina VII. This reflected feedback pathway has a role in modulating noxious (pain) signals within the dorsal horn through endorphins (Chap. 9).

Norepinephrine is present in the neurons of the locus ceruleus and nucleus subceruleus (Chap. 13). The noradrenergic projections from these nuclei to the spinal cord descends in the ventrolateral funiculus and terminates in laminae I, II, V, VII, and IX.

These aminergic pathways have roles in (1) influencing preganglionic sympathetic neurons in the spinal cord, (2) exerting facilitatory activity on the level of responsiveness of the lower motoneurons, (3) modulating the relative intensity of various expressions of emotional states, and (4) modulating noxious stimuli associated with pain (Chap. 9).

Functional Groups of the Somatic Motor (Descending Pathways)

In a general way, each of the descending tracts of upper motoneurons can be placed into one of three functional groups: (1) lateral group, (2) anteromedial group, and (3) aminergic group.

1. The *lateral group* (lateral *descending tract systems),* comprises the lateral corticospinal and rubrospinal tracts. It terminates in lateral portions of the ventral horn and the intermediate zone of the spinal gray matter. Within the spinal gray matter are anatomic linkages involved primarily in the control of voluntary movements associated with the limbs, especially with distal limb musculature. The corticospinal tract originates primarily from the primary motor cortex (area 4), supplementary motor cortex (area 6) and parietal lobe (areas 1, 2, 3, 5, and 7). The rubrospinal tract originates from the magnocellular portion of the nucleus ruber. Because these tracts decussate, they act on the side opposite their sites of origin. Functionally, the lateral pathways have a critical role in the fine manipulative and independent movements of the extremities, especially of the hands and feet. They are involved in the *fractionation of movement* as is expressed in the ability to control and execute independent finger movements. More specifically, fractionation is the ability to control, for example, an individual muscle of the hand independently of other muscles involved with normal manual dexterity. The fibers of the lateral corticospinal tract that terminate directly on the alpha motoneurons have a major role in effecting the expression of fractionation of movements. Following a lesion to this tract, there is a diminution or loss of fractionation. The rubrospinal tract, although small in humans, can be clinically significant; it could account for certain residual motor function that persists after a lesion of the corticospinal tract.

   Those fibers of the corticospinal tract originating in the parietal lobe (areas 1, 2, 3, 5, and 7) are components of the *reflected feedback pathways*, noted previously; these fibers terminate in the dorsal horn, where they modulate sensory input.
2. The *anteromedial group* (medial *descending tract systems)*, comprises the anterior corticospinal tract, lateral and medial reticulospinal tracts, lateral and medial vestibulospinal tracts, and tectospinal tract. These tracts terminate in the medial part of the ventral horn and intermediate zone, which provides anatomic linkages for c*oordinated activity of the axial and limb girdle musculature during postural movements*. These tracts exert bilateral control because (1) most contain both crossed and uncrossed fibers and (2) they terminate on interneurons that have axons that cross over to the opposite side. This can account for minimal loss of motor control of axial musculature following unilateral lesions to these tracts, in which limb control is profoundly affected. Many of these descending tracts terminate in the cervical and upper thoracic levels; hence, they preferentially control neck,

upper trunk and shoulder girdle musculature, rather than lower trunk and hip girdle musculature.

The anterior corticospinal tract is involved with voluntary movements associated with axial muscles of the neck and trunk. The reticulospinal tracts, which receive a major input from the premotor cortex, are thought to be involved in the more automatic, involuntary movements of the axial and limb musculature involved with posture and locomotion. They can be significant in controlling girdle musculature. The lateral vestibulospinal tract that descends as an uncrossed tract throughout the entire length of the spinal cord is critical in the maintenance of balance (Chap. 16). The medial vestibulospinal tract, which is a caudal extension of the MLF, descends bilaterally; it is involved with orienting head position through coordinating the activity of the neck and back musculature. The tectospinal tract originates from the deep layers of the superior colliculus, an important structure that receives input from the visual system. This tract is presumed to be involved with coordinating head and neck movements with eye movements.

The anteromedial pathways exert their influences on musculature bilaterally. Even such uncrossed tracts as the lateral vestibulospinal and reticulospinal tracts do so by terminating on interneurons, some of which emit axons that decussate in the anterior commissure to the opposite side.

The fibers of these upper motoneuron control pathways exert their effects by (1) direct synaptic connections with lower motoneurons and (2) synaptic connections with interneurons that are integrated with local circuits influencing lower motoneurons. Thus, the activity of lower motoneurons is controlled by direct and indirect polysynaptic connections from the upper motoneurons and, in addition, from sensory input from spinal nerves to the reflex circuits (Chap. 8).

3. The *aminergic pathways* modulate the excitability of the spinal neuronal circuits involved with regulating the activity of lower motoneurons.

VOLUNTARY MOVEMENTS

The spinal cord, brainstem, and forebrain possess sequentially the three essential features of motor circuitry (from reflexes to rhythmic motor patterns to complex voluntary movements). The command center for these activities is organized as a motor hierarchy with the spinal cord at a *lower level* comprising a sequence of neuronal circuits mediating a variety of reflexes and basic movement rhythms (Chap. 6) A *higher level* of motor hierarchy is in the brainstem with its control of rhythmic automatisms. The two motor systems originating at this level are (1) the medial descending systems and (2) the lateral descending systems (noted previously). The medial systems contribute to posture control by modulating the axial and limb girdle musculature, whereas the lateral systems control the more distal limb musculature and their important goal-directed movements, especially of the forearm and hand. The cortex of the forebrain mediates voluntary motor control at the highest level. The primary motor cortex and some premotor areas project (1) via the corticospinal tract directly to the anterior horn of the spinal cord and (2) via corticobulbar fibers regulate the motor tracts originating in the brainstem.

Voluntary purposeful movements, such as the sequence of motions resulting in catching a ball, involve several cortical areas, including the (1) primary motor cortex (area 4), (2) premotor cortex (area 6), (3) supplementary motor cortex (area 6), and (4) posterior parietal cortex (areas 5 and 7) (*see* **Fig. 25.3**). The following is an outline of a current concept of the interrelation of these cortical areas involved in the initiation of complex volitional movements. The appreciation of the spatial coordinates of the object of interest (ball) involves the posterior parietal lobe (Chap. 25). This information is conveyed via axons terminating in the primary motor cortex, premotor cortex, and supplementary motor cor-

tex, which process these inputs into their circuitry. These motor cortices have specific roles that interact to produce a sequence of coordinated movements that lead to catching the ball. Both the premotor cortex and the supplementary motor cortex project somatotopically to the primary motor cortex. In turn, the supplementary motor cortex receives a critical input from the basal ganglia via a projection from certain neurons in the ventral lateral (VL) nucleus of the thalamus. The premotor cortex receives a major input from the cerebellum via a projection from another group of neurons in the VL. Details of the functional aspects of these inputs are presented in Chapters 18 and 24.

A motor program constitutes sequence of movements directed to a purposeful goal (e.g., a plan of action to catch a ball). This includes the selection and coordination of the muscles involved in the sequence of all the movements of the entire action. The *posterior parietal lobe* contributes processed sensory information that is essential for guiding the movement to the goal. The *premotor cortex* and the *supplementary motor cortex* are involved in the planning and programming of the complex sequences and guidance of the movements and also contribute information to affect the output of area 4. The *premotor cortex* exercises a primary role in regulating the axial and proximal limb musculature essential in the initial phases of orientating the body and lower limb toward the goal and the upper limb in an appropriate position. The *supplementary motor cortex* exerts a role in the complex movements of the proximal limb musculature and, in addition, simultaneous movements of the limbs of both sides of the body. The *motor cortex (area 4)* has an essential role in the control of the distal muscles of the extremities, especially in the dexterity, skill, and agility of finger movements. The precise control of individual fingers (and even toes in some individuals) is the result of the fractionation of muscle contractions.

The motor areas give rise to corticospinal and corticobulbar fibers to the brainstem and spinal cord. These areas also give rise to corticorubral fibers to the ipsilateral red nucleus and to corticoreticular fibers to the brainstem reticular nuclei of both sides.

SUGGESTED READINGS

Asanuma H. *The Motor Cortex*.New York: Raven; 1989.

Bock G, Goode J, eds. *Sensory Guidance of Movement.* New York: Wiley; 1998.

Brooks VB. *The Neural Basis of Motor Control.* New York: Oxford University Press; 1986.

Capaday C. The special nature of human walking and its neural control. *Trends Neurosci.* 2002; 25:370–376.

Dietz V. Human neuronal control of automatic functional movements: interaction between central programs and afferent input. *Physiol. Rev.* 1992; 72:33–69.

Dum RP, Strick PL. Motor areas in the frontal lobe of the primate. *Physiol. Behav.* 2002;77:677–682.

Everts E. Role of motor cortex in voluntary movements in primates. In Brooks VE, ed. *Handbook of Physiology.* Bethesda, MD: American Physiological Society; 1981;1083–1120.

Fukunaga T, Kubo K, Kawakami Y, Fukashiro S, Kanehisa H, Maganaris CN. In vivo behaviour of human muscle tendon during walking. *Proc. R. Soc. Lond. B. Biol. Sci.* 2001;268:229–233.

Georgopoulos AP. New concepts in generation of movement. *Neuron.* 1994;13:257–268.

Georgopoulos AP. Cognitive motor control: spatial and temporal aspects. *Curr. Opin. Neurobiol.* 2002;12:678–683.

Grillner S. Neural networks for vertebrate locomotion. *Sci. Am.* 1996;274:64–69.

Grillner S. The motor infrastructure: from ion channels to neuronal networks. *Nature Rev. Neurosci.* 2003;4:573–586.

Grillner S, Wallen P. Innate versus learned movements—a false dichotomy? *Prog. Brain Res.* 2004;143:3–12.

Halsband U, Freund HJ. Motor learning. *Curr Opin Neurobiol.* 1993;3:940–949.

Lam T, Pearson KG. The role of proprioceptive feedback in the regulation and adaptation of locomotor activity. *Adv Exp Med Biol.* 2002; 508:343–355.

Lieber R. *Skeletal Muscle Structure, Function, & Plasticity: The Physiological Basis of Rehabilitation.* 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2002.

Lieber RL, Friden J. Clinical significance of skeletal muscle architecture. *Clin Orthop.* 2001;383: 140–151.

MacNeilage PF, Davis BL. Motor mechanisms in speech ontogeny: phylogenetic, neurobiological and linguistic implications. *Curr. Opin. Neurobiol.* 2001;11:696–700.

McCrea DA. Spinal circuitry of sensorimotor control of locomotion. *J Physiol.* 2001;533:41–50.

Pearson K. Motor systems. *Curr Opin Neurobiol.* 2000;10:649–654.

Phillips C. Movements of the hand. Liverpool: Liverpool University Press; 1986.

Rizzolatti G, Luppino G. The cortical motor system. *Neuron.* 2001;31:889–901.

Rothwell J. *Control of Human Voluntary Movement.* 2nd ed. New York: Chapman & Hall; 1994.

Ungerleider LG, Doyon J, Karni A. Imaging brain plasticity during motor skill learning. *Neurobiol. Learn. Mem.* 2002;78:553–564.

Wiesendanger M, Wise SP. Current issues concerning the functional organization of motor cortical areas in nonhuman primates. *Adv. Neurol.* 1992;57:117–134.

Wing A, Haggard P, and Flanagan J. *Hand and Brain: The Neurophysiology and Psychology of Hand Movements.* San Diego: Academic; 1996.

Wise SP. The primate premotor cortex fifty years after Fulton. *Behav. Brain Res.* 1985;18:79–88.

12
Lesions of the Spinal Nerves and Spinal Cord

Release Phenomena
Lesions of the Ventral Roots
Lesions of the Dorsal Roots
Lesions of the Upper Motoneurons (Upper Motoneuron Paralysis, Spastic Paralysis)
Symptoms of Value in Localizing Lesions to Spinal Levels
Spinal Cord Hemisection (Brown's Quard Syndrome)
Spinal Cord Transection
Intrinsic Arterial Supply to the Spinal Cord
Lesion in the Region of the Central Canal (Syringomyelia)
Tabes Dorsalis
Amyotrophic Lateral Sclerosis
Combined System Degeneration
Degeneration, Regeneration, and Sprouting

Injuries to the nervous system, as well as neurologic diseases, produce symptoms and clinical signs. This chapter outlines some effects of lesions of the spinal nerves and spinal cord. The term *lesion* refers to pathologic and traumatic tissue damage. Ensuing impairments include the loss or modification of function related to the injury.

RELEASE PHENOMENA

The signs associated with a lesion of the nervous system are manifested by two types of abnormal function or capacity: (1) with negative signs or (2) with positive signs.

Negative signs are expressed as the loss of a function or capacity as the result of a lesion. Examples are the loss of strength of a muscle, or its inability to contract (motor), or the loss of a sensation such as touch or sight (sensory).

Positive signs are expressed as abnormal motor responses (motor) or bizarre sensations (sensory). A positive sign is usually the expression of a *release phenomenon*. It results from the withdrawal (release) of inhibitory influences from normal neural circuitry that mediates a normal response or capacity. Inhibitory circuits act as a governor that modulates, shapes, and controls the excitatory circuits from becoming overactive (*see* Importance of Inhibition, Chap. 3). A lesion incapacitates the regulating inhibitory influences that the injured regulator exerted on a released neural circuit. Release phenomena are expressed (1) in the abnormal movements in Parkinson's disease and Huntington's chorea, both of which are associated with lesions in the basal ganglia (Chap. 24), or (2) as the distorted pain sensations of the thalamic syndrome (Chap. 23) or in the phantom limb (Chap. 9).

LESIONS OF THE VENTRAL ROOTS

Depending on the specific spinal level, lesions of the ventral roots interrupt specific alpha and gamma motoneurons and pregan-

glionic autonomic fibers (*see* **Fig. 12.1**, nos. 1 and 2a). The injury of all the lower motoneurons innervating a muscle or group of muscles results in a lower motoneuron paralysis or paresis of that muscle or muscles. This occurs in poliomyelitis—the polio virus can selectively affect lower motoneurons of the spinal cord and of the brainstem. When preganglionic autonomic fibers are injured, trophic effects can accompany the lower motoneuron paralysis.

Lower Motoneuron Paralysis (Flaccid Paralysis)

The signs of a *lower motoneuron (flaccid) paralysis* and associated trophic changes include the following:

1. All voluntary movements are abolished, and reflex contractions cannot be elicited when all of the lower motoneurons innervating a group of muscles are interrupted. The muscles are paralyzed. A *paresis* (partial paralysis, weakness) results when some, but not all, of the lower motoneurons normally innervating the muscle remain functional.
2. The paralyzed muscles have lost their tone; therefore, they are flaccid and offer little resistance to manipulation by the examiner. Because the myotatic reflex arcs are not intact, the deep tendon reflexes (DTRs) are absent (*areflexia*). If some of the lower motoneurons are functional, the tonus is reduced (*hypotonus*) and the DTRs are weak (*hyporeflexia*).
3. Reaching a peak about 2–3 weeks following denervation, muscles spontaneously contract. In time, the muscles atrophy. The spontaneous contractions of muscle fibers are known as fibrillations and fasciculations. *Fibrillation* is a single muscle fiber twitching, which can be seen only when the affected muscle is thinly covered, as in the tongue and, rarely, in the hand. It can be detected by electromyographic examination. Fibrillation is a response associated with the hypersensitivity of a denervated muscle (Chap. 20). *Fasciculation* is a muscle twitching visibly through the skin, resulting from the spontaneous discharge of a motor unit. As a lower motoneuron dies, it discharges repetitively to produce fasciculations of the muscle fibers it innervates.
4. The trophic changes include dry, cyanotic skin, which can be ulcerated.

Trophic Functions and Changes

The autonomic nervous system includes a motor system involved with influencing the activities of the involuntary (smooth) muscles, cardiac (heart) muscle, and glands (Chap 20). In contrast, the somatic motor system is involved with influencing voluntary (skeletal, striated) muscles. In addition to stimulating muscles to contract and glands to secrete, both the autonomic and somatic motor systems exert effects that initiate and regulate the molecular organization of other cells. These effects are expressions of the *trophic* (literally *nutritional*) functions of the nervous system.

Trophic influences by neurons are directed to different types of target tissue, including the epithelium, nerve endings (e.g., taste buds), and muscle cells. Following lesions of fibers of the autonomic nervous system, trophic changes include the following: a warm or cool, flushed or cyanotic skin, as a result of changes in capillary circulation; abnormal brittleness of fingernails; loss of hair; dryness or ulceration of the skin; and lysis of the bones and joints.

The atrophy that occurs in skeletal muscles deprived of their lower (somatic) motoneuron innervation is more profound than the atrophy following disuse. Another effect on the skeletal muscle fibers in the former case stems from the loss of trophic influences that are essential for the maintenance of the normal condition. Fibrillation is another expression of a change in trophic influences.

Myasthenia Gravis: An Autoimmune Disease

Myasthenia gravis is a muscle weakness disability that is associated with defects of transmission at the motor end-plate junctions between nerve endings and the voluntary muscle acetylcholine receptors (ACh receptors).

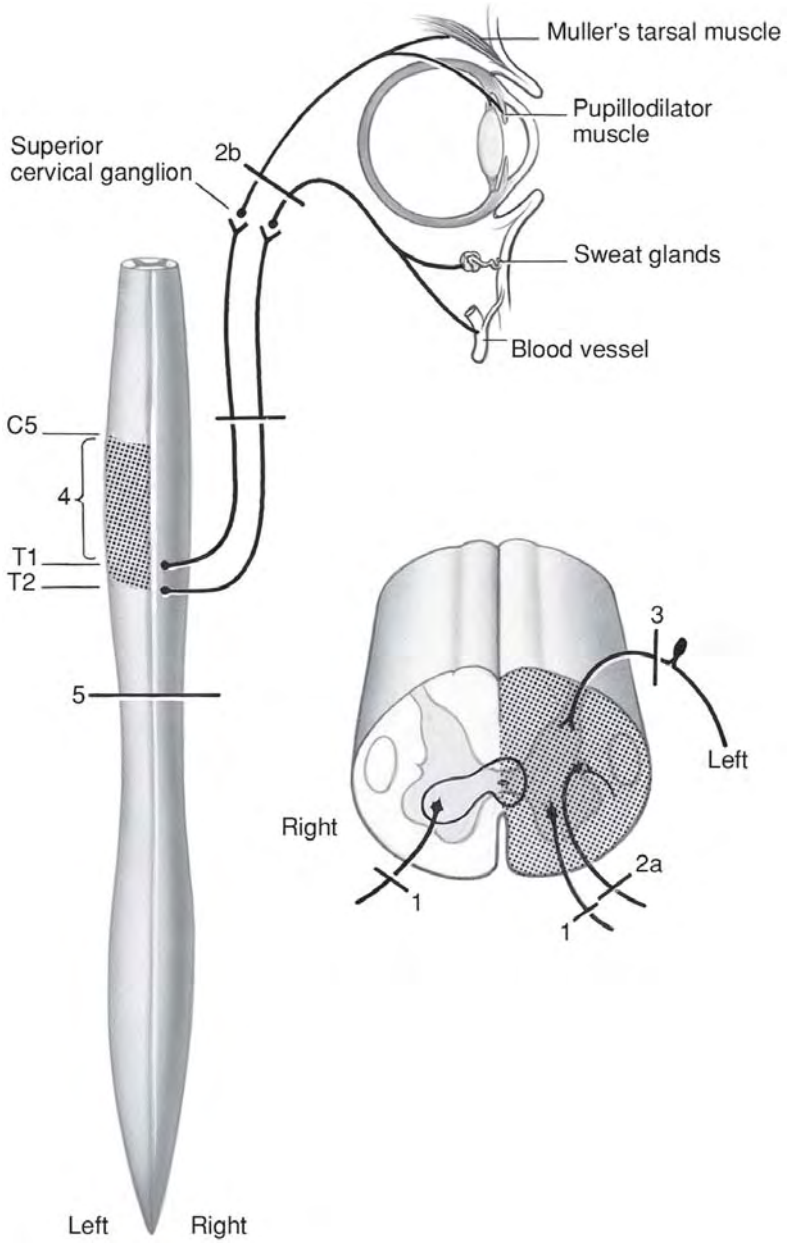


Figure 12.1. Schemata of the spinal cord to indicate the sites of lesions noted in the text. Arabic numbers refer to specific lesions. C5 to T1 indicate the cervical enlargement, the region involved with innervation of the upper extremity. 1, ventral roots of spinal nerves; 2a, preganglionic sympathetic fibers from T1 to T2 levels; 2b, postganglionic sympathetic fibers from the superior cervical ganglion; 3, dorsal roots of spinal nerves; 4, hemisection of the spinal cord (Brown–Séquard syndrome) extending through the cervical enlargement (stippled region); 5, transection of the spinal cord at a midthoracic level; 6, lesion in region surrounding central canal throughout the cervical enlargement and extending into the anterior horn at the C8 and T1 level on one side.

The defect is caused by an antibody-mediated attack, which reduces the number of nicotinic ACh receptors and is accompanied by sparse and shallow junctional folds and widened clefts of the postsynaptic membrane (sarcolemma) (Chap. 15; and **Fig. 2.5**). As a consequence, there is a reduction in the probability of evoking an action potential in the sarcolemma. This neuromuscular disease is characterized by a marked fatigability and weakness of the voluntary muscles that is improved by inhibitors of cholinesterase such as physostigmine. Thus, by inhibiting the degradation of acetylcholine at the motor end plate, the time is prolonged for the available transmitter to act on the remaining receptors.

The critical symptom of the affliction is weakness of voluntary muscles. Characteristic features include double vision resulting from a decrease in the coordination of the extraocular muscles, drooping eyelids (weak levator palpebrae muscles), and weakness of the limb muscles. Intense activity of a muscle will rapidly lead to severe fatigue. In myasthenia gravis, lymphocyte T-cells generated in the thymus gland become activated to react against the ACh receptors. The antibodies inactivate the ACh receptors as fast or faster than they can be synthesized for replacement. The normal turnover of ACh receptors is about 5–7 days. With the increased destruction of ACh receptors in myasthenia gravis, the turnover rate is increased to 2–4 days. The therapeutic effects of thymectomy relates to the immunological role of the thymus. Following thymectomy, about one-half of patients with myasthenia gravis go into "remission," showing no symptoms even without drug therapy.

Horner's Syndrome

Horner's syndrome occurs as a consequence of a lesion to certain fibers of the sympathetic division of the autonomic nervous system. With regard to Horner's syndrome, the critical sympathetic components are *preganglionic fibers* that emerge from T1 and T2 spinal cord segments and terminate in the superior cervical ganglion, which is located alongside the spinal column. Unmyelinated *postganglionic fibers* arising from the superior cervical ganglion follow arterial blood vessels and have synaptic terminals on sweat glands, smooth muscle that dilates the pupils of the eyes, smooth muscles of the cutaneous blood vessels, and smooth muscle (called the tarsal muscle or Muller's muscle) of the upper eyelid (*see* **Fig. 12.1**).

Lesions of preganglionic sympathetic fibers from T1 and T2, or of postganglionic sympathetic fibers from the superior cervical ganglion, will result in *Horner's syndrome* on the ipsilateral side of the face (*see* **Fig. 12.1**, nos. 2a and 2b). The affected pupil is smaller than the pupil of the opposite eye; it does not dilate (miosis) when the pupil is shaded (pupillodilator smooth muscle unit is not stimulated to contract). The affected eyelid droops a bit (ptosis) because the superior palpebral smooth muscle (Muller's muscle) is denervated. The face is dry (anhydrosis from denervated sweat glands), red, and warm (vasodilatation of cutaneous blood vessels). This is the memorable triad of symptoms: miosis, ptosis, and anhydrosis.

LESIONS OF THE DORSAL ROOTS

The irritation of the fibers of one dorsal root (radix) by mechanical compression (tumor or slipped disk) or a local inflammation can produce pain with a radicular distribution (*see* **Fig. 12.1**, no. 3). Because adjacent dermatomes overlap, the destruction of one dorsal root (e.g., by transection) can result in slight diminution of all sensations (*hypesthesia*) in part of the dermatome innervated by that dorsal root. Destruction of several consecutive dorsal roots does result in the complete absence of all sensations (*anesthesia*) in all but the rostral and caudal dermatomes innervated by the sectioned roots. Irritation to the dorsal root fibers can result in *paresthesia* (abnormal spontaneous sensations such as numbness and prickling) or *hyperalgesia* (excessive pain in response to an

otherwise innocuous stimulus). The stimulation of a dorsal root can result in a *dermatomal vasodilatation* (because of reflex arcs involving the autonomic nervous system).

If all dorsal roots innervating the upper extremity (C5 through T1) are transected (e.g., surgically by dorsal root rhizotomy), several symptoms can be additionally observed. Because the afferent limb of the reflex arcs is interrupted, reflex activity is absent (areflexia) and muscles are hypotonic. Although the limb muscles are not paralyzed (lower motoneurons are intact), motor activity is impaired. The deafferented limb hangs by the side and is generally not used. It can be volitionally moved when facilitatory influences from the descending supraspinal motor pathways stimulate the lower motoneurons. Because the lower motoneurons remain intact and functional, there is little or no loss in muscle strength and no occurrence of fasciculations. There is some disuse atrophy, but because trophic influences are not lost, there is no trophic atrophy.

Lesions and irritations of the dorsal roots or posterior horn cause segmental (dermatomal) sensory disturbances. In dorsal root lesions, all general senses in the region innervated by the root fibers (dermatome) are lost or diminished. In posterior horn lesions, a *dissociated sensory loss* (loss of one sensation and the preservation of others) can occur in the dermatome, with, for example, pain and temperature sensibilities lost or reduced, but touch and other associated general senses intact and normal. Dissociated sensory loss of pain and temperature also occurs in lesions in the vicinity of the central canal (*see* Lesions in the Region of the Central Canal).

Following an injury restricted to one dorsal root, no area of anesthesia is revealed in the dermatome innervated because of the overlap from fibers of adjacent dorsal roots. Such an injury, however, can produce so-called radicular (a root is a radix) pain that is localized in the dermatome innervated by that root; such patients are aware of a tingling pain or even a diminished feeling of sensation or numbness.

LESIONS OF THE UPPER MOTONEURONS (UPPER MOTONEURON PARALYSIS, SPASTIC PARALYSIS)

Interruption of the upper motoneurons results in motor disturbances known as an *upper motoneuron paralysis*. The lesion in the genu and posterior limb of the internal capsule that results in the most typical constellation of upper motoneuron (UMN) lesion signs involves the corticobulbar, corticospinal, corticorubrospinal, and corticoreticulospinal pathways. Often the symptoms of an UMN lesion are attributed to a lesion of the corticospinal tract; but actually other UMN pathways also contribute to the symptoms, including the circuitry of the cortical–basal ganglia loops (Chap. 24). Apparently, the only neurologic sign associated exclusively with a corticospinal tract lesion is the Babinski sign (*see* later in this section).

Immediately after the onset of a lesion in the internal capsule (*see* **Fig. 1.8**), the patient develops a paralysis of the lower muscles of facial expression (below the level of the eye) and of the upper and lower limb musculature (hemiplegia) on the opposite side of the body. The lower facial muscles are paralyzed if the lesion is in the genu and damages the corticobulbar fibers passing through (Chap. 11).

As a rule, following a unilateral corticobulbar lesion, all voluntary muscles innervated by cranial nerves, except those of facial expression below the eye, are spared. This is because the lower motoneurons to all of the other muscles of facial expression receive bilateral corticobulbar innervation, but the lower motoneurons to muscles of facial expression below the eye receive corticobulbar innervation only from the contralateral side of the cerebral cortex (Chap. 11). Therefore, a unilateral lesion will lead to paralysis on the opposite side.

In the limbs, deep tendon (stretch) reflexes are temporarily depressed and the muscles exhibit hypotonia. In time, from a few days to a few weeks, the stretch reflexes return and then become hyperactive. Muscle tone increases

to hypertonia. The expression of hyperreflexia by the muscles is called spasticity and the muscles are said to be spastic. The basic cause for the spasticity is not fully understood. One explanation is that the UMN lesions reduce inhibitory influences upon both the gamma and alpha motoneurons more than they do excitatory influences. This is accompanied by hypersensitive dynamic gamma motoneurons, which stimulate the muscle spindles to increase their rate of discharge and, thus, increase the activity of the stretch reflex. Other evidence suggests that the spasticity is primarily the result of hyperactive alpha motoneurons because of the "filling in" of degenerated UMN synapses by sprouting of local segmental afferent fibers.

An upper motoneuron paralysis is called a *spastic paralysis*. Such a paralysis of the upper and lower limbs on one side is called a *hemiplegia* (less than total hemiparesis). The clinical signs of an UMN paralysis include increased muscle tone (hypertonia), increased deep tendon (stretch) reflexes (hyperreflexia), clonus, loss or diminution of cutaneous reflexes, and the Babinski reflex (sign). Spasticity is thought to result from damage to UMN pathways other than the corticospinal tract; selective damage to the pyramids in the medulla of laboratory animals produces decreased, not increased, muscle tone.

1. *Hypertonus* is expressed in the firmness and stiffness of muscles—primarily in the flexors of the upper limb and in the extensors of the lower limb. These are antigravity muscles; the upper limbs are held up by the contraction of flexors, and the lower limbs support the body by contraction of extensors. This increased resistance (hypertonus) to passive movement is expressed as the examiner tries to flex or extend each limb. The brisk knee jerk following the tapping of the quadriceps muscle tendon is an example of *hyperreflexia*. The spastic body parts exhibit increased resistance to manipulation, especially the flexors of the upper limbs and the extensors of the lower limbs. However, if the force exerted by an examiner persists, the resisting muscles yield suddenly in a *clasp knife* fashion. The sudden yielding of resistance is ascribed to a surge of afferent input from group II fibers from the muscle spindles and also possibly from C pain fibers from low-threshold pain receptors and, according to some, from the Ib fibers from Golgi tendon organs.
2. *Clonus* is the rhythmic oscillation of a joint (e.g., ankle or knee) that occurs when a second party suddenly dorsiflexes the foot (light pressure on the sole of foot pushes toes toward knee) and maintains the dorsiflexion attitude under continuous light pressure. The dorsiflexion puts the gastrocnemius muscle, its muscle spindles, and the Achilles tendon under moderate stretch. The resulting stretch reflex contraction of the gastrocnemius produces plantar flexion of the foot. This is accompanied by stretching of the tibialis anterior and other dorsiflexor muscles of the foot and their muscle spindles. The resulting stretch reflex contraction of the tibialis anterior produces a dorsiflexion of the foot. The cycle repeats. Clonus persists as long as the gastrocnemius is kept in a moderate state of contraction by elastic pressure.
3. Superficial reflexes that normally are elicited by stroking certain areas of the skin might be absent if the corticospinal tract is injured. When the skin of the abdominal wall is gently scratched, the abdominal muscles contract and the resulting reflex diverts the umbilicus momentarily toward the stimulated site. Stroking the upper inner aspect of the thigh normally causes a reflex contraction of the cremasteric muscle and elevation of the testicle on the stimulated side. Loss of the *abdominal* or *cremasteric reflexes* confirms the presence of a corticospinal tract lesion. (Absence of these reflexes bilaterally in an otherwise normal individual might have no significance.)
4. The *Babinski reflex* (sign) can be elicited. When the lateral aspect of the sole of the foot is stroked with a blunt point, the great toe dorsiflexes (hyperextension), the tip of the toe points to the knee, and the other toes

spread (fan),—called the extensor plantar response.

The finding of a Babinski sign in newborns and infants up to a year or so of age is not an indication of an upper motor neuron lesion, but rather of incomplete central nervous system (CNS) development—the corticospinal tract is not completely myelinated.

SYMPTOMS OF VALUE IN LOCALIZING LESIONS TO SPINAL LEVELS

Symptoms with a dermatomal distribution are associated with a specific dorsal root or roots. Furthermore, symptoms that show signs of lower motoneuron paralysis are associated with a specific ventral root or roots. For example, (1) a band of anesthesia with a dermatomal distribution results from the destruction of specific dorsal root fibers; (2) paresthesias or radicular (root) pain with a dermatomal distribution results from irritation of fibers in specific dorsal roots; the skin eruption and hyperalgesia expressed in a dermatomal pattern known as *shingles* is caused by a dorsal root ganglion infected by *herpes zoster virus*; (3) flaccid paralysis and other lower motoneuron signs result from the destruction of motoneuron cells and fibers in the anterior horn or ventral roots.

SPINAL CORD HEMISECTION (BROWN'S QUARD SYNDROME)

A hemisection (unilateral transverse lesion) of the spinal cord results in a number of changes in the body at that level or caudal to it (*see* **Fig. 12.1**, no. 4). For instructional purposes, assume that the lesion is a hemisection extending from C5 through T1 spinal levels; the peripheral nerves associated with these spinal levels innervate the upper extremity. In the nervous system, in relating the side of a lesion (right or left) to the side of the body where signs are expressed, the site where a pathway decussates must be considered with regard to the location of the lesion. (1) Symptoms occur on the same side (ipsilateral) and below the level of the lesion when the damaged neurons normally convey influences from the same side of the body (ascending sensory tract) or to the same side of the body (descending motor tracts). In the spinal cord, structures involved with ipsilateral functions include the posterior column, dorsal roots, lateral corticospinal tract, rubrospinal tract, reticulospinal tracts, and ventral roots. (2) Symptoms occur on the opposite (contralateral) side below the level of the lesion when the damaged neurons convey information from or to the opposite side of the body. In the spinal cord, this includes the decussated fibers of the anterolateral pathway and the lateral and the anterior spinothalamic tracts. In the brainstem this includes the spinothalamic tract, medial lemniscus, and corticospinal tract.

When the fiber tracts are injured, the resultant symptoms and signs include the following:

1. At the spinal levels of transection (C5 through T1), the entering fibers of the dorsal roots and the emerging fibers of the lower motoneurons and preganglionic sympathetic fibers (C8 and T1) are interrupted. This results in a complete absence of all sensations in the upper extremity on the side of lesion. Pain and temperature are lost on the contralateral upper extremity because of interruption of the postdecussational fibers of the lateral spinothalamic tract. Paresthesias and radicular pain can be sensed over the ipsilateral C5 and T1 dermatomes from the irritation of some intact dorsal root fibers; because of dermatome overlap from C4 and T2, the C5 and T1 dermatomes have a hypesthesia. The entire ipsilateral limb is flaccid; it exhibits all of the signs of a lower motoneuron paralysis. Horner's syndrome on the ipsilateral side of the face and trophic changes in the ipsilateral upper extremity are the result of the interruption of the preganglionic sympathetic neurons.

2. *Posterior column (fasciculi gracilis and cuneatus)*. The signs are loss of position sense, appreciation of passive movement, vibratory sense, and two-point discrimination on the same side at and below the levels of the lesion. The modalities from the neck are unaffected because fibers conveying them are located wholly above the level of the lesion. Ataxia (stumbling and staggering gait) associated with injury of the posterior column cannot be observed because of the paralysis.
3. *Lateral spinothalamic tract*. The sign is loss of pain and temperature on the opposite side at and below the levels of the lesion. This includes the contralateral upper extremity because lateral spinothalamic fibers decussate within one or two levels of the spinal root origin.
4. *Anterior spinothalamic tract*. Touch sensibility is probably little affected on the opposite side below the spinal level of the lesion because this modality is also conveyed in the uncrossed fasciculi gracilis and cuneatus.
5. *Corticospinal tract and other descending supraspinal tracts*. The spastic syndrome following the interruption of these fibers results in an upper motoneuron paralysis, including spasticity, hyperactive deep tendon reflexes (DTRs) (hyperreflexia), diminution or loss of superficial reflexes, Babinski sign, and muscle clonus below (but not at level of) the site of lesion on the ipsilateral side. The hyperactive DTRs are illustrated by a brisk knee jerk or ankle jerk.

SPINAL CORD TRANSECTION

Paraplegia

Complete transection of the spinal cord at a midthoracic level (*see* **Fig. 12.1**, no. 5) because of a traumatic event causes immediate *paraplegia* together with a loss of detectable neural activity caudal to the lesion site. *Paraplegia* is a paralysis of both lower limbs resulting from interruption of the UMNs on both sides of the spinal cord.

All voluntary movements and somatic and visceral reflex activities are abolished. Sensations from the body below the transection level are absent. This period of extremely depressed activity, called *spinal shock* lasts about 2–3 weeks in man (it varies in duration from 4 days to 6 weeks). Spinal shock is apparently the result of the sudden withdrawal of facilitatory influences from the descending pathways, especially the corticospinal tract.

The isolated spinal cord and its spinal nerves gradually exhibit autonomous neural activity that is divided into a sequence of phases of variable lengths: (1) minimal reflex activity, (2) flexor spasm activity (superficial reflexes), (3) alternation between flexor and extensor spasms, and (4) predominant extensor spasms (deep reflexes). After a year or two, paraplegics can fit one of several categories: (1) that in which extensor spasms predominate over flexor spasms, called *paraplegia-in-extension* (observed in about two-thirds of paraplegics); (2) that in which flexor spasms predominate, called *paraplegia-in-flexion*; and (3) that in which a flaccid paralysis persists (less than 20%). The absence of autonomic nervous system impulses from the brain is accompanied by a variety of disturbances in the control of automatic activities of the urinary, genital, and anorectal systems.

Loss of thermoregulatory control below the level of the lesion is expressed with a cool, dry skin with no evidence of sweating (Chap. 20). However, reflex sweating can occur when a noxious stimulus is applied (e.g., response to the insertion of the needle during a spinal tap). There is loss of voluntary control of the urinary bladder. The urinary bladder can be evacuated by reflex activity such as by appropriate cutaneous stimulation.

Quadriplegia

Quadriplegia is the paralysis of all four limbs and is associated with a transection of the spinal cord in or above the region of the cervical enlargement. Because of dermatomal and myotomal overlap, patients with T1 injuries have normal hand function. Transections above

C3 eliminate descending control of the diaphragm, requiring a respirator; the phrenic nerve arises mainly from C3, but the adjoining segments usually contribute. *Monoplegia* involves paralysis of one limb.

INTRINSIC ARTERIAL SUPPLY TO THE SPINAL CORD

In general, two arteries and their branches supply the spinal cord (*see* **Fig. 12.2**). Branches of the unpaired anterior spinal artery vascularize the anterior two-thirds of each spinal segment. The branches of the paired posterior spinal arteries supply the remainder of the spinal cord.

The *anterior spinal artery syndrome* results in signs resulting from bilateral injury to the anterior horns, anterolateral pathways, and lateral corticospinal (pyramidal) tracts. The symptoms occur suddenly and are often associated with severe pain. Flaccid paralysis, fasciculations, and atrophy bilaterally at the segments involved are the result of lesions in the anterior horns (lower motoneuron paralysis). Spastic paralysis below the level of the lesions results from bilateral lesions of the descending motor tracts (upper motoneuron paralysis). Pain and temperature sensibilities might be lost bilaterally below the level of a thrombosis because of involvement of the anterolateral pathways, but might be spared if adequate blood is supplied by the posterior spinal arteries.

LESION IN THE REGION OF THE CENTRAL CANAL (SYRINGOMYELIA)

Syringomyelia is a disease characterized by formation of a syrinx (cavity) in the region of the central canal probably caused by incomplete closure of the central canal; with time, the cavitation can enlarge and extend to other sites (*see* **Fig. 12.1**, no. 6). Assuming, as commonly occurs, that the lesion is located in the cervical enlargement (from C5 to T1 spinal cord levels), the initial clinical signs are a loss of pain and

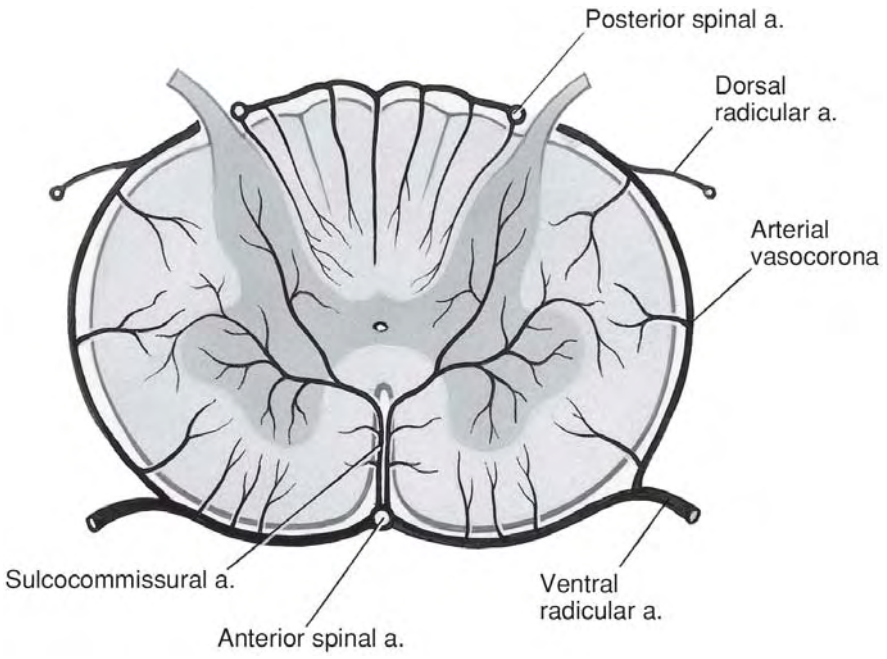


Figure 12.2: The arterial supply of the spinal cord.

temperature sensibility in both upper limbs. The loss is the result of the interruption of the decussating pain and temperature fibers as they pass through the anterior white commissure, conveying information from both upper limbs. Proprioception and light touch are nowhere affected because the posterior columns are intact. There is no loss of pain and temperature sensation in the body and lower limbs because the anterolateral pathway (except for fibers from the upper limb) remains intact.

Extension of the lesion into the anterior horn of C8 and T1 spinal levels on one side produces ipsilateral lower motoneuron disturbances and trophic changes on the ulnar side of the arm, forearm, hand, and fourth and fifth fingers, as well as a possible Horner's syndrome because the ulnar nerve originates from C8 to T1 levels, as do the preganglionic sympathetic fibers to the superior ganglion.

TABES DORSALIS

Tabes dorsalis is a form of neurosyphilis in which the primary pathology of the dorsal root ganglia is accompanied by secondary degenerative changes in the posterior columns, especially in the fasciculi gracilis bilaterally. Pain fibers are also involved. In the initial stages, the irritation of dorsal root fibers produces paresthesias and intermittent attacks of sharp pain. In time, the symptoms include diminished sensitivity to pain, loss of kinesthetic sense, diminished-to-absent deep tendon reflexes (ankle and knee jerks), loss of muscle tone, and marked impairment of muscle, joint, and vibratory senses accompanied by an ataxic gait. Patients walk with legs wide apart, head bent, and eyes looking down, raising their knees high and slapping their feet on the ground. The eyes stare at the ground to pick up visual cues, which substitute for the lost kinesthetic senses.

As in ataxia, a patient with tabes dorsalis exhibits Romberg's sign (i.e., the inability to stand with eyes closed and feet together without swaying or actually falling). With the eyes open, an afflicted person might be able to keep upright by using visual cues to compensate for loss of proprioception.

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is a degenerative motor tract disease with bilateral involvement of the pyramidal tracts and anterior horns. Because there is degeneration of both upper and lower motoneurons, signs of both upper and lower motoneuron paralysis are expressed. Most of the affected muscles show evidence of degeneration of lower motoneurons, including paralysis, atrophy, fasciculations, and weakness; these signs are initially expressed by the muscles of the hands and arms. Some muscles exhibit signs of upper motoneuron paralysis, hyperreflexia, and, at times, Babinski signs. The lower motoneurons of cranial nerves might also exhibit signs of degeneration. Sensory changes do not usually occur.

COMBINED SYSTEM DEGENERATION

Combined system degeneration is a complication of pernicious anemia (a disease caused by a lack of intrinsic factor for absorption of vitamin B_{12}) in which there is subacute degeneration bilaterally of the fibers of the posterior columns and lateral columns, especially those involved with the lumbosacral cord. The clinical symptoms include (1) loss of position and vibratory senses, numbness, and dysesthesia in the lower extremities and (2) such upper motoneuron signs as spasticity, muscle weakness, hyperactive deep tendon reflexes, Babinski reflexes and Romberg's sign.

DEGENERATION, REGENERATION, AND SPROUTING

An injured neuron reacts to an insult, whether it is a transection, a crush, a toxic substance, or a deprivation of blood supply. The entire neuron

responds and, depending on location and circumstances, might survive (*see* **Fig. 2.11**).

Degeneration

The degenerative reactions following transection include changes in (1) the cell body (chromatolysis), (2) the nerve fiber between the cell body and the trauma (primary degeneration), and (3) the nerve fiber distal to the trauma (secondary, anterograde, or Wallerian degeneration). The cell body swells, Nissl bodies undergo "dissolution" or chromatolysis, and the nucleus is displaced to the side of the cell body. These are manifestations of metabolic activities, which can ultimately lead to the regeneration of the severed fiber. Chromatolysis is indicative of enhanced protein synthesis. Degenerative changes in the nerve proximal to the cut include breakdown of the myelin sheath and axon in the vicinity of the injury. The axon and myelin sheath of the fiber distal to the trauma become fragmented and are removed by macrophages, usually over a period of weeks.

Nerve Regeneration in the Peripheral Nervous System (*see* Fig. 2.11)

Regeneration is essentially a process of differentiation and growth. The cell bodies synthesize proteins and other metabolites that flow distally into the regenerating and lengthening axons. The neurolemma (Schwann) cells in the proximal stump near the trauma, and in the distal stump, they divide mitotically to form continuous cords of neurolemma cells. These cords extend from the proximal stump, through the small gap between the stumps into the distal stump, and to the sites of sensory receptors for afferent fibers and motor endings for efferent fibers. In addition, the ends of the proximal axons branch into numerous sprouts that grow distally at about 4 mm per day into the gap and distal stump along the neurolemmal cords to the sites of the nerve endings. Each regenerating axon of the proximal stump can divide to form as many as 50 terminal sprouts. In turn, each neurolemmal cord can act as the guiding scaffold for numerous regenerating axons. The surviving regenerating axons are those that terminate in the proper nerve endings. The potential of each neurolemmal cord to act as a guide for many regenerating axons increases the possibility of reinnervating the appropriate receptor or effector. When fully myelinated, each regenerating branch tends to have a conduction velocity of about 80% of that of the original fiber. Superfluous axonal branches eventually degenerate.

Collateral Sprouting. A denervated neurolemmal cord is presumed to exert trophic influences upon a nearby normal nerve fiber; the latter responds by sprouting new collateral branches from its nodes of Ranvier. This is known as *preterminal axonal sprouting* or *collateral nerve sprouting*. The collateral branch joins the axonless neurolemmal cord, grows down the cord, and reinnervates the nerve ending. Collateral nerve sprouting occurs in both the peripheral nervous system and central nervous system, but the latter does not have neurolemmal cords (*see* **Fig. 2.11**).

Regeneration in the Central Nervous System

Loss of neurons occurs normally throughout life. This neuronal loss is generally accompanied by a compensatory sprouting of axonal branches by other CNS neurons in the vicinity. Many of these axonal sprouts invade the territory previously innervated by the dead neuron and form new synapses. This activity, known as *reactive synaptogenesis*, is an attempt to replace lost synapses. Molecular and trophic factors, which enhance this process, were discussed in Chapter 2. The release of a neurotrophic factor by Schwann cells can be the critical factor that promotes this growth and regeneration in the peripheral nervous system.

Neurons of fetal and neonatal mammals have a great capacity for regeneration. This is the logic of transplanting young neurons into the brains of adult mammals to attain some degree of functional recovery following dysfunction. Transplantation of fetal dopaminergic neurons into the striatum in patients with Parkinson's disease is being carried out in an attempt to obtain some clinical recovery (Chap. 24).

SUGGESTED READINGS

Barbeau H, Fung J. The role of rehabilitation in the recovery of walking in the neurological population. *Curr. Opin. Neurol.* 2001;14:735–740.

Barbeau H, Ladouceur M, Norman KE, Pepin A, Leroux A. Walking after spinal cord injury: evaluation, treatment, and functional recovery. *Arch Phys Med Rehabil.* 1999;80:225–235.

Brodal A. Self-observations and neuroanatomical considerations after a stroke. *Brain* 1981;96: 675–694.

Collins R. *Neurology.* Philadelphia: Saunders; 1997.

Dietz V, Colombo G, Jensen L, Baumgartner L. Locomotor capacity of spinal cord in paraplegic patients. *Ann. Neurol.* 1995;37:574–582.

Hohmann GW. Some effects of spinal cord lesions on experienced emotional feelings. *Psychophysiology* 1966;3:143–156.

Hohmann GW. Considerations in management of psychosexual readjustment in the cord injured male. *Proc. Veterans Admin. Spinal Cord Inj. Conf.* 1971;18:199–204.

Hohmann GW. Psychological aspects of treatment and rehabilitation of the spinal cord injured person. *Clin. Orthop.* 1975;Oct(112):81–88.

Kalb RG, Strittmatter SM, eds. *Neurobiology of Spinal Cord Injury.* Totowa, NJ: Humana; 2000.

Lance J, McLeod JG. *A Physiological Approach to Clinical Neurology.* 3rd ed. Boston: Butterworth; 1981.

McLeod J, Lance J. *Introductory Neurology.* Boston: Blackwell Scientific; 1989.

Nathan PW. Effects on movement of surgical incisions into the human spinal cord. *Brain* 1994; 117(Pt. 2):337–346.

Rossignol S. Locomotion and its recovery after spinal injury. *Curr. Opin. Neurobiol.* 2000;10:708–716.

Sunderland S. *Nerves and Nerve Injuries.* Edinburgh: Livingstone; 1978.

Sunderland S. *Traumatized Nerves, Roots and Ganglia: Musculoskeletal Factors and Neuropathological Consequences.* New York: Plenum; 1978.

Tepper MS, Whipple B, Richards E, Komisaruk BR. Women with complete spinal cord injury: a phenomenological study of sexual experiences. *J. Sex Marital Ther.* 2001;27:615–623.

13
Brainstem: Medulla, Pons, and Midbrain

Longitudinal Organization of the Brainstem
Surface Landmarks
Brainstem Cranial Nerves
Functionally Significant Internal Landmarks
Transverse Sections Through the Brainstem

The role of the brainstem is divisible into three broad categories. The first is to provide transit and processing nuclei for ascending and descending pathways that convey influences to and from the cerebrum, cerebellum, and spinal cord. The second is to play a part in a range of activities such as consciousness, the sleep–wake cycle, and respiratory and cardiovascular control. The third relates to actions of the cranial nerves, which are comprised of sensory fibers terminating in brainstem nuclei and motoneurons originating in brainstem nuclei.

LONGITUDINAL ORGANIZATION OF THE BRAINSTEM

The brainstem is longitudinally organized into three regions: (1) the roof, posteriorly, (2) the base or basilar portion, anteriorly, and (3) the tegmentum in the center. The ventricular cavity is located between the tegmentum and the roof (*see* **Fig. 13.1**).

Roof

The posterior boundary of the brainstem is known as the *roof*. In the midbrain, the roof is called the *tectum* (quadrigeminal plate). The cerebellum (not a brainstem structure) serves as the roof of the pons, and the tela choroidea and its choroid plexus form the roof of the medulla. The tectum includes the pretectum (light reflex; Chap. 18), superior colliculus (optic reflexes; Chap. 18), inferior colliculus (auditory system; Chap. 16), and the emerging trochlear nerve (n.IV) caudally (*see* **Figs. 13.2 and 13.3**).

Basilar Portion

The basilar portion is called the *crus cerebri* (pes pedunculi) in the midbrain, *basilar pons* or *pons proper* in the pons, and *pyramids* in the medulla (*see* **Fig. 13.4**). The basilar portion consists of descending pathways originating in the cerebral cortex. These include (1) corticobulbar and corticoreticular fibers, which terminate in the tegmentum, and the corticospinal tract, which terminates in the spinal cord, and (2) corticopontine fibers (to pontine nuclei of the basilar pons); pontocerebellar fibers, which form the middle cerebellar peduncle, take origin from the pontine nuclei (Chap. 18).

Tegmentum

The tegmentum extends throughout the entire length of the brainstem (*see* **Fig. 13.1**). Major structures within the tegmentum include (1) the reticular formation, which forms the central core of the tegmentum, (2) pathways such as the posterior column–medial lemniscus, anterolateral system (spinothalamic tract), trigeminal pathways, medial longitudinal fasciculus, and auditory pathways, (3) cerebellar relay nuclei and tracts, and (4) cranial nerve nuclei and roots of 10 cranial nerves. The *central tegmental tract,* equivalent to the spinospinalis tracts of the spinal cord, is the intrinsic tract of the tegmentum. This tract, containing

fibers of mixed origins and terminations, conveys influences both rostrally and caudally.

Ventricular Cavity

The ventricular cavity includes the cerebral aqueduct (of Sylvius) in the midbrain and the fourth ventricle in the pons and rostral medulla, which continues caudally as the central canal.

SURFACE LANDMARKS

The cerebral structures illustrated in **Figs. 13.2–13.5** include the *third ventricle, thalamus* (Chap. 23), *pineal body* (Chap. 21) of the *diencephalon*, the *stria terminalis* of the *limbic system* (Chap. 22), the *internal capsule, corona radiata, lentiform nucleus, caudate nucleus, olfactory nerve* and *trigone*, and *optic nerve* and *tract* of the *cerebrum* (Chaps. 22–24). The location of the emergence of the cranial nerves from the brain is discussed in Chapter 14.

Posterior Surface (*see* Figs. 13.2, 13.3)

The roof of the midbrain consists of the *corpora quadrigemina (tectum)* that include the paired *superior colliculi (optic system)* and the paired *inferior colliculi (auditory system)*. The

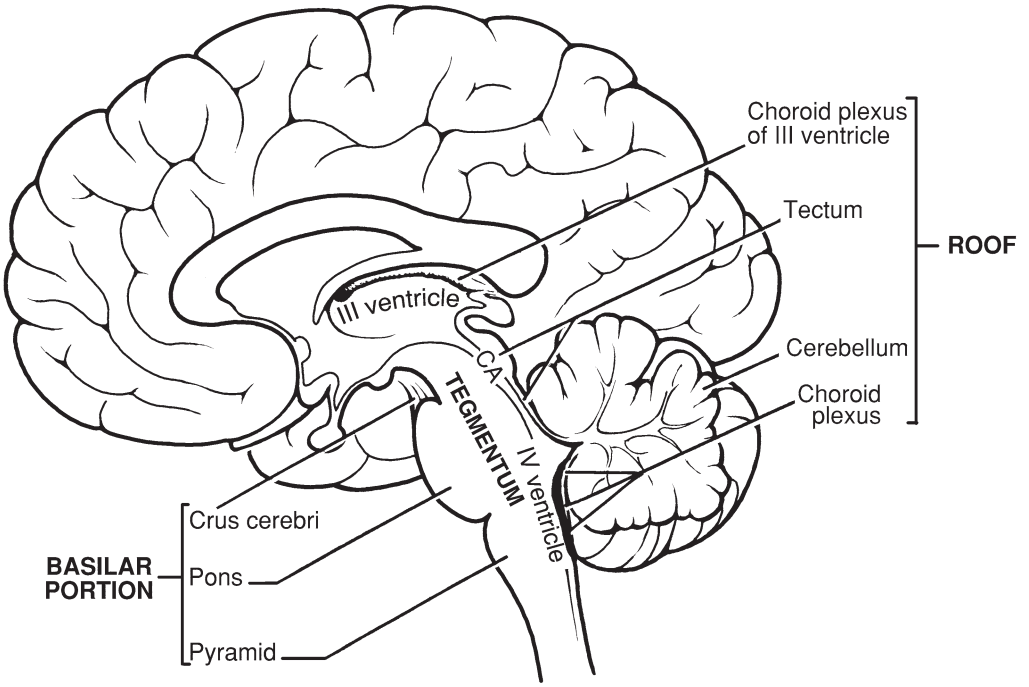


Figure 13.1: Median sagittal section of the cerebrum and brainstem to illustrate the longitudinal stratification of the latter into (1) roof, (2) ventricular portion (3) tegmentum, and (4) basilar (ventral) portions. The roof consists of the tectum (including superior and inferior colliculi), inferior medullary velum, cerebellum, and choroid plexus of the fourth ventricle. The ventricular portion consists of the cerebral aqueduct (CA), fourth (IV) ventricle, and the central canal in the caudal medulla, and it is continuous rostrally with the third ventricle in the diencephalon**.** The tegmentum occupies the core of the three brainstem subdivisions and includes the reticular formation with its nuclei and pathways, cranial nerves and their nuclei, sensory and cerebellar relay nuclei, the ascending lemniscal pathways, and so forth. The basilar portion comprises the crus cerebri, the basilar portion of the pons, and the medullary pyramids. (Refer to Figs 1.1 and 1.5.)

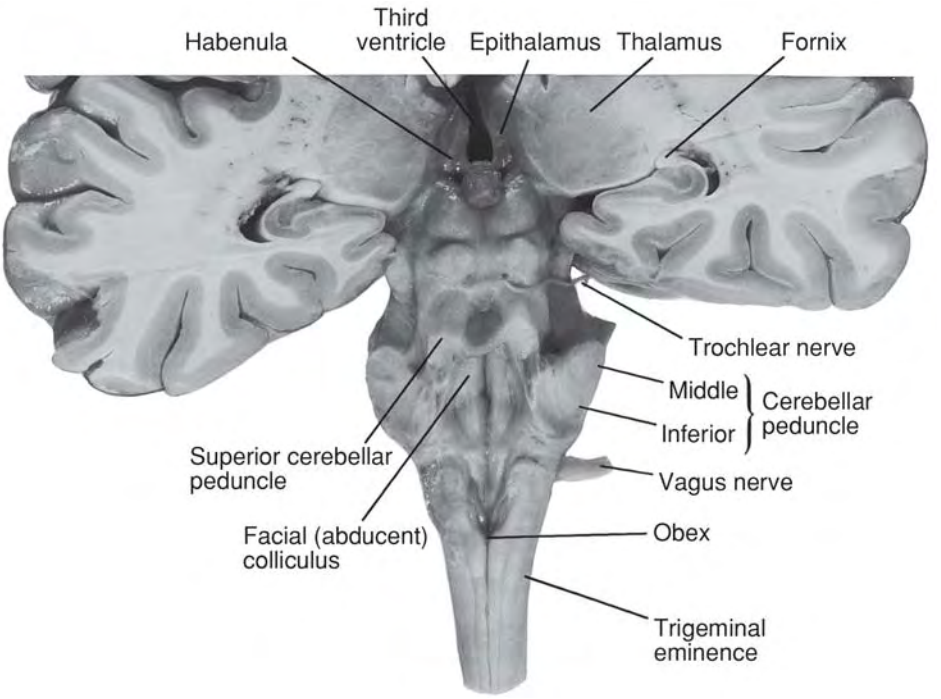


Figure 13.2: Photograph of the posterior (dorsal) surface of the brainstem. Compare with Fig. 13.3. (Courtesy of Dr. Howard A. Matzke.)

superior colliculus and the *pretectum* are associated with visual guidance and tracking activities related to eye and head movements, as well as the light reflex and accommodation (Chap. 19). The inferior colliculus is part of the auditory pathway, as is the brachium of the inferior colliculus, which consists of fibers connecting the inferior colliculus with the medial geniculate body of the thalamus (Chap. 16). The lateral geniculate body is a thalamic nucleus of the visual pathways (Chap. 19). The trochlear nerve (n.IV) emerges caudal to the inferior colliculi.

The roof (cerebellum and tela choroidea of the fourth ventricle) of the pons and medulla has been removed, showing structures on the floor of the ventricle, as well as out laterally the cut surface of the three pairs of cerebellar peduncles: *inferior, middle,* and *superior cerebellar peduncles* (*see* **Figs. 13.2 and 13.3**). The floor of the fourth ventricle, which is the roof of the tegmentum, contains the *facial colliculus (abducent colliculus)* formed by the underlying abducens nucleus and genu of the facial nerve (*see* **Fig. 13.12**). The area vestibularis, trigonum vagi, and trigonum hypoglossi (*see* **Fig. 13.3**) are eminences formed by the underlying vestibular nuclei, dorsal vagal nucleus and hypoglossal nucleus, respectively (*see* **Figs. 13.10 and 13.11**). The tuberculum cuneatus, tuberculum gracilis, and olive (*see* **Fig. 13.3**) are protuberances formed by the nucleus cuneatus, nucleus gracilis, and inferior olivary nucleus of the medulla, respectively (*see* **Fig. 13.9**). The obex is a fold of tissue dorsal to the site where the fourth ventricle funnels into the central canal; it is used as a neurosurgical landmark.

Basal Surface (*see* Fig. 13.4)

The oculomotor nerve (n.III) emerges from the interpeduncular fossa located between the

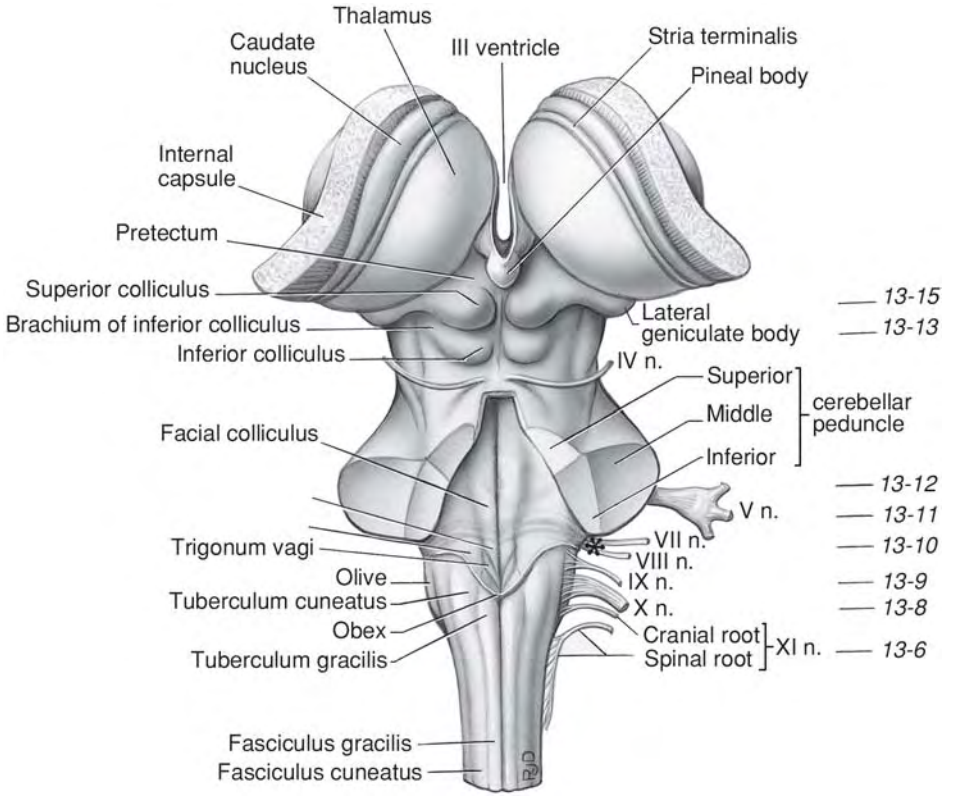


Figure 13.3: Posterior surface of the brainstem. Lines adjacent to the figure indicate the levels of the transverse sections illustrated in Figs. 13.6–13.15. Roman numerals represent cranial nerves visible in this view.

crus cerebri of the cerebral peduncles of the midbrain (*see* **Figs. 13.15 and 13.16**). Note that (1) cranial nerve V emerges laterally from the midpons, (2) cranial nerves VI, VII, and VIII emerge from medial to lateral along the junction between the pons and medulla, (3) cranial nerves IX, X, and XI emerge in a rostral to caudal continuum from the postolivary sulcus dorsal to the olive, and (4) cranial nerve XII emerges from the preolivary sulcus between the olive and pyramid. The pyramids are paired columns formed by the pyramidal (corticospinal) tracts.

Lateral Surface (*see* Fig. 13.5)

Note that the rootlets (1) of cranial nerves 1S, S, and X1 emerge for the goove that is dorsal to the olive and (2) of cranial nerve X11 from the groove that is ventral to the olive.

Most structures labeled in this view have been noted earlier. The great majority of fibers that form the superior cerebellar peduncle originate in the dentate nucleus of the cerebellum. The olive is formed by the underlying inferior olivary nucleus.

BRAINSTEM CRANIAL NERVES

Cranial nerves III through XII emerge from the brainstem (*see* **Figs. 13.3 and 13.4**). Arising from the basal surface slightly lateral to the midline are n.III (oculomotor) from the interpeduncular fossa, n.VI (abducent) at the pons–medulla junction, and n.XII (hypoglossal) as filaments from the preolivary sulcus located between the inferior olive and medullary pyra-

mid. Cranial nerve IV (trochlear) emerges from the posterior surface of the caudal midbrain (*see* **Figs. 13.2 and 13.3**).

The remaining cranial nerves arise from the lateral surface of the brainstem. They include n.V (trigeminal) from the midpons, n.VII (facial) and n.VIII (vestibulocochlear) from the pons–medulla junction, and n.IX (glossopharyngeal), n.X (vagus) and n.XI (cranial root of spinal accessory nerve) as nerve filaments from the postolivary sulcus. The spinal root of n.XI arises as filaments emerging laterally between the dorsal and ventral roots of spinal cord levels C1 to C6 (*see* **Fig. 13.4**).

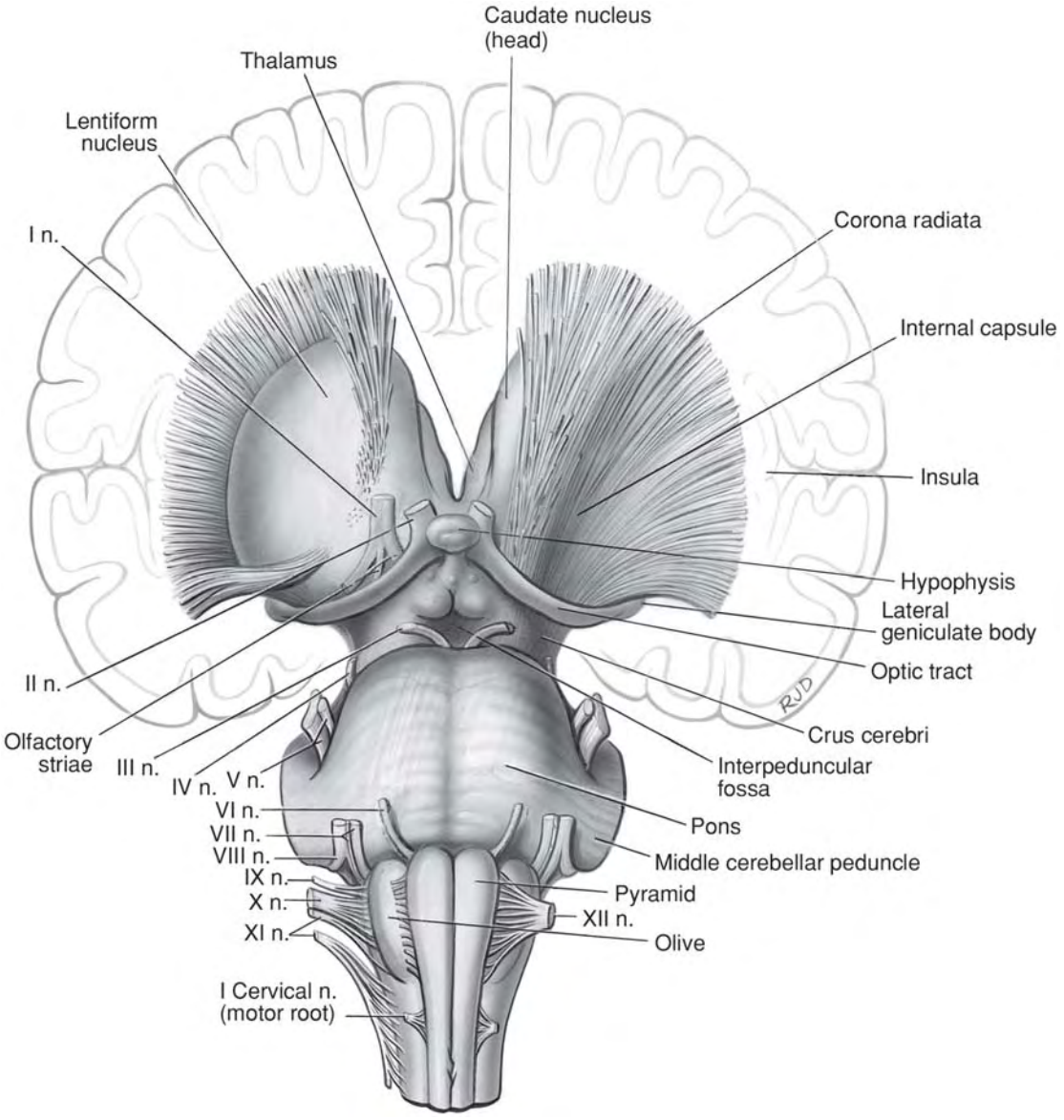


Figure 13.4: Basal surface of the brainstem and roots of cranial nerves.

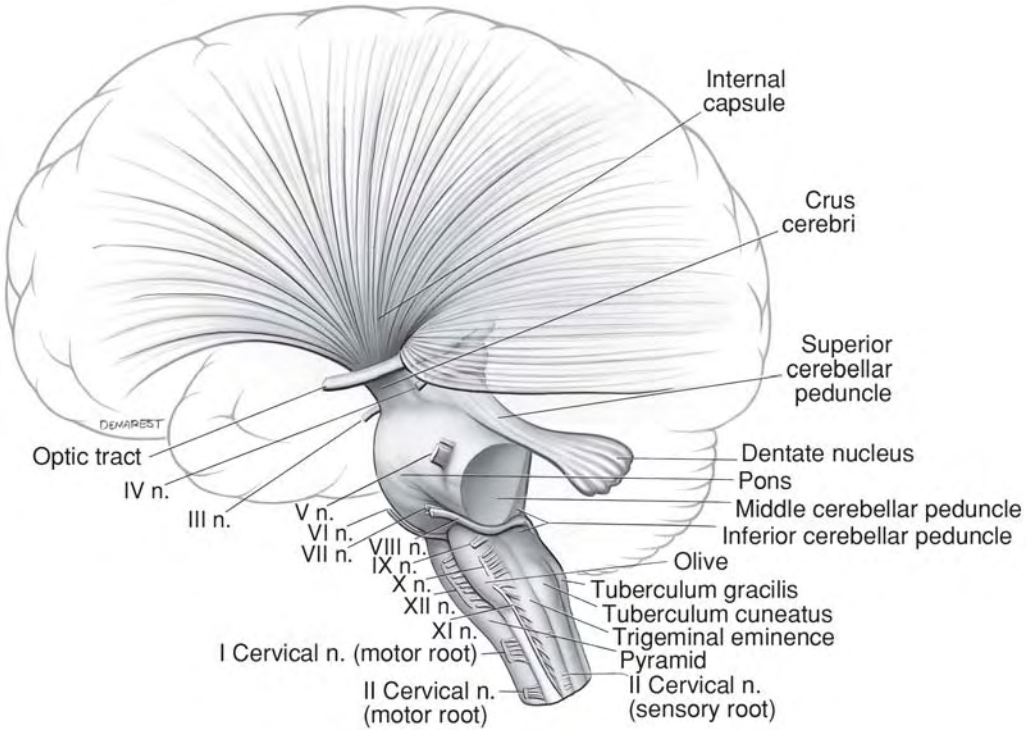


Figure 13.5: Lateral surface of the brainstem and roots of cranial nerves.

FUNCTIONALLY SIGNIFICANT INTERNAL LANDMARKS

The internal anatomy of the brainstem can be visualized by appreciating the topographic relations of some major tracts and cranial nerves.

Corticopontine, Corticobulbar, and Corticospinal Tracts

These tracts, originating from the cerebral cortex, descend successively through the internal capsule, crus cerebri, and basilar pons (*see* **Figs. 13.4 and 13.5**). The corticopontine fibers terminate in the pontine nuclei. Along their course, corticobulbar fibers terminate in neuronal pools, influencing cranial nerve nuclei located within the tegmentum (*see* **Figs. 13.8 to 13.16**). The corticospinal tracts continue as the pyramids of the medulla. They cross the midline as the decussation of the pyramidal tract at the junction between the brainstem and spinal cord (*see* **Fig. 13.8**) and enter the lateral columns of the spinal cord (*see* **Fig. 11.2**).

Posterior Column–Medial Lemniscus Pathway (See Chap. 10)

The fasciculi gracilis and cuneatus terminate in the nucleus gracilis (forming the tuberculum gracilis) and nucleus cuneatus (forming the tuberculum cuneatus) (*see* **Figs. 13.3 and 13.9**). Fibers from these nuclei decussate as the internal arcuate fibers in the lower medulla to form the medial lemniscus (*see* **Fig. 13.9**), which ascends through the tegmentum and terminates in the ventral posterolateral nucleus of the thalamus (*see* **Fig. 10.3**). As the medial lemniscus ascends, it gradually shifts from an anteromedial location in the medulla to a posterolateral position in the midbrain (*see* **Figs. 13.9 to 13.16**).

Anterolateral Pathway (See Chap. 9)

This pathway ascends from the spinal cord and continues within the lateral aspect of the tegmentum as the spinothalamic tract until it terminates in the ventral posterolateral nucleus of the thalamus (*see* **Figs. 9.2, 13.7 to 13.9, and 13.12 to 13.16**).

Trigeminal Pathways

The trigeminal nerve enters the brainstem laterally in the midpons (*see* **Figs. 13.4 and 14.5**). Some of its primary fibers descend as the spinal tract of n.V, which forms a ridge, the *trigeminal eminence* (*see* **Fig. 13.2**). Some second-order fibers arising from the principal sensory nucleus and spinal nucleus of n.V decussate to form the anterior trigeminothalamic tract, which is located between the medial lemniscus and the spinothalamic tract in the pons and midbrain; nondecussating fibers form the posterior trigeminothalamic tract), located posterolaterally in the tegmentum (*see* **Figs. 10.6, 13.13, and 13.14**). Both tracts of trigeminothalamic fibers terminate in the ventral posteromedial nucleus of the thalamus.

Medial Longitudinal Fasciculus

This bundle, which contains fibers from multiple sources, extends from the midbrain through the spinal cord, although most of the fibers originating in the brainstem do not descend beyond cervical levels. In the brainstem, the medial longitudinal fasciculus (MLF) is located anterior to the cerebral aqueduct and the fourth ventricle and on either side of the midline (*see* **Figs. 13.10 to 13.16**). It shifts position slightly in the lower medulla (*see* **Fig. 13.8**). The MLF contains fibers that are critical for the execution of synergistic (conjugate) eye movements (Chap. 16) and with adjustments for alterations in head position.

Auditory Pathways (See Chap. 16)

Auditory pathways receive afferent input from the cochlear nuclei located on the surface of the inferior cerebellar peduncle in the rostral medulla (*see* **Fig. 13.11**). The auditory pathways ascend as the *lateral lemniscus*, located in the lateral tegmentum just ventromedial to and interdigitating with the spinothalamic tract (*see* **Fig. 13.13**). The fibers of the lateral lemniscus terminate in the *inferior colliculus* (*see* **Fig. 13.14**), which gives rise to the *brachium of* the *inferior colliculus*. The brachium terminates in the medial geniculate body of the thalamus (*see* **Figs. 13.15 and 13.16**).

Spinocerebellar and Pontocerebellar Tracts

The spinocerebellar pathways are located in the lateral tegmentum of the brainstem (*see* **Fig. 10.7**). The posterior spinocerebellar tract and the cuneocerebellar tract from the accessory cuneate nucleus enter the cerebellum via the inferior cerebellar peduncle (*see* **Figs. 13.10 to 13.12**). The anterior spinocerebellar tract ascends to the lower midbrain and passes through the superior cerebellar peduncle (*see* **Fig. 13.13**). Fibers from the pontine nuclei decussate as pontocerebellar fibers and form the middle cerebellar peduncle (*see* **Figs. 13.13, 13.14, and 18.3**). The three pair of cerebellar peduncles (*see* **Fig. 13.3**) gives access to the entire cerebellum.

Reticular Formation

The brainstem tegmentum consists of (1) nuclei and fibers of cranial nerves (Chap. 14), (2) long tracts of sensory and motor pathways (Chaps. 9 o 11), (3) nuclei and tracts related to the cerebellum (Chap. 18), and the (4) reticular formation.

The reticular formation (RF) is the central or reticular core of the tegmentum. It is an intricate neural network composed of reticular nuclei (*see* **Fig. 13.6**), ascending reticular pathways, descending reticular pathways, and local reflex circuits of cranial nerves. Phylogenetically older than most of the other surrounding structures, the RF consists of a diffuse yet organized network of nuclei and tracts (hence, the term *reticular*). The RF network consists of multipolar neurons with long ascending and descending axons, which have highly collateralized branches synaptically linked with interneurons into complex loops of circuits

(Chap. 22; *see* **Fig. 22.1**). The brainstem RF is an anatomical component of the *reticular system* (Chap. 22).

The brainstem component of the reticular system exerts significant modulatory effects on the activities of the spinal cord, brainstem, and cerebrum, including the cerebral cortex. The ascending reticular pathways include the reticular activating system, which is involved with sleep–wake cycles and in modulating awareness. The descending reticular pathways express their roles in motor activities as manifest in behavioral performances. The nuclei of the RF are organized in three longitudinal zones: (1) median raphe zone, (2) medial reticular zone, and (3) lateral reticular zone (*see* **Fig. 13.6**).

Some of the brainstem reticular nuclei are arranged in distinct groups. On the basis of neural connections and the biochemical nature of their neurotransmitters, they form three major aminergic (monoaminergic) systems or pathways: (1) noradrenergic (transmitter is norepinephrine), (2) dopaminergic (transmitter is dopamine), and (3) serotonergic (transmitter is serotonin) systems (*see* **Figs. 15.2 and 15.3**).

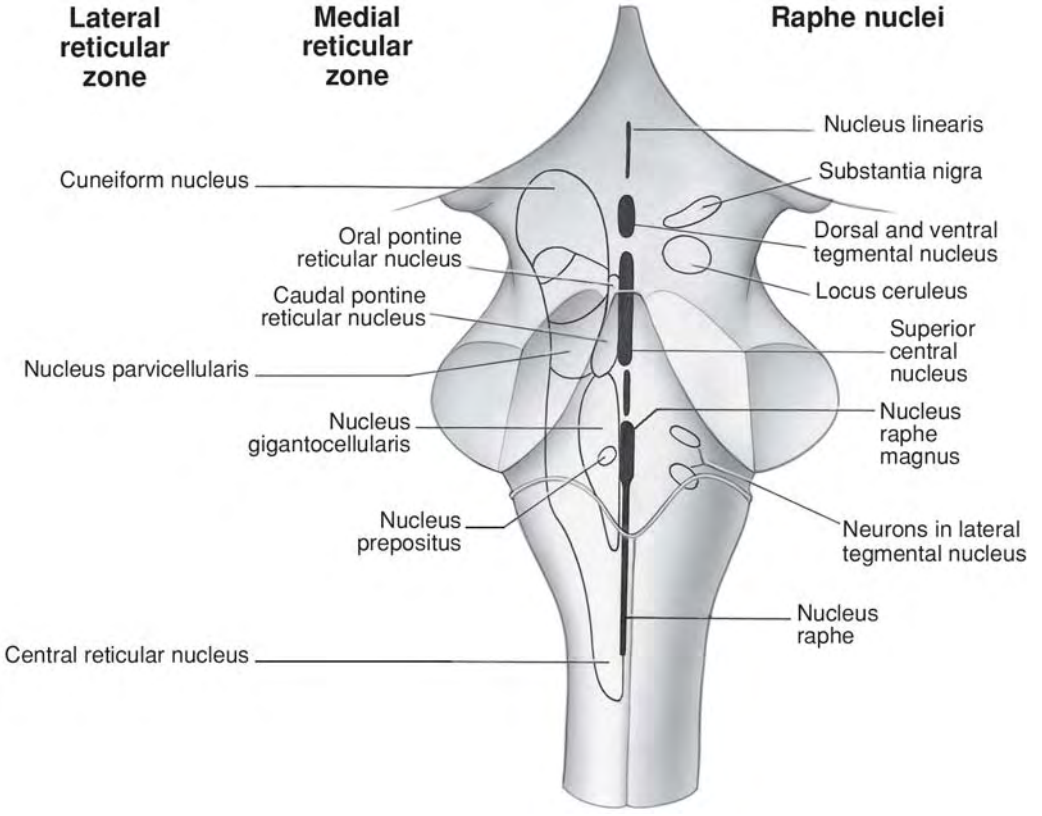


Figure 13.6: Posterior view of the brainstem illustrating some of the nuclei of the reticular formation. Nuclei of the lateral and medial reticular zones are noted on the left, and the raphe nuclei, locus ceruleus, and noradrenergic lateral tegmental nuclei on the right, together with the substantia nigra. Refer to Figs. 13.7–13.16. The reticular nuclei projecting to the cerebellum (e.g., lateral reticular nucleus and pontine reticulotegmental nucleus) are not included. Nu., nuclei; Ret., reticular. (Adapted from DeMyer.)

Noradrenergic System. Noradrenergic neurons, which characterize the locus ceruleus (LC), a nucleus in the upper pons (*see* **Fig. 13.14**), also form scattered cell groups in the lateral tegmentum of the pons and medulla (*see* **Fig. 13.6**).

The locus ceruleus (cerulean blue color in the fresh human brainstem) receives major input from nuclei in the vicinity of the nucleus gigantocellularis. The axon of each LC neuron has a T-like bifurcation, forming ascending and descending branches that are more widely distributed than those of any other known nucleus (*see* **Fig. 15.2**). The axons profusely collateralize into fibers that sprout thousands of branches, which are distributed directly to the thalamus, hypothalamus, hippocampus, cerebral cortex, cerebellum, and the dorsal and ventral horns of the spinal cord (*see* **Fig. 15.2**). Axons arising from the other tegmental adrenergic neurons are primarily distributed to the brainstem and spinal cord and have lesser projections to the thalamus, cerebral cortex and cerebellum. Catecholamine pathways with their diffuse connections modulate numerous functions, rather than initiating or mediating specific ones. They play a role in phases of the sleep–wake cycle. When activated by novel or intense sensory stimuli, the locus ceruleus helps coordinate preparation of appropriate responses. The lateral tegmental neurons exert their roles in the autonomic nervous system by evoking a decrease in arterial pressure and heart rate. To be specific about what functions are evoked is complicated for the following reason. The modulatory activity of the circuits can produce differences and nuances in physiological and behavioral expressions because of the variety of ways inputs can be biased—dependent on the degree of stimulation (or inhibition) of excitatory (or inhibitory) neurons in the complex circuitry.

Serotonergic System. Serotonergic neurons in the brainstem outnumber those of the adrenergic and dopaminergic systems. The cell bodies of the neurons of this extensive system are located at the midline in the raphe nuclei (*see* **Fig. 13.6**). Neurons of the raphe nuclei in the upper pons and midbrain project via the median forebrain bundle to the oculomotor nuclei, substantia nigra, striatum, hypothalamus, limbic structures such as the hippocampus, and the cerebral cortex. Neurons of the nucleus raphe magnus have fibers projecting locally to the facial nucleus and caudally to the sensory dorsal horn and the motor ventral horn of the spinal cord.

The widespread connections of this system are expressed by its modulatory and augmenting role, rather than by a specific behavior. It functions in enhancing learning of avoidance behavior and in increasing the excitability of lower motoneurons. Inhibitory roles are expressed in the dorsal horn of the spinal cord by modulating and repressing pain, producing analgesia, and increasing the pain threshold (Chap. 9). This system can also participate in initiating sleep. This is consistent with insomnia that occurs following experimental destruction of the raphe nuclei.

Dopaminergic System. Dopaminergic neurons are present in the substantia nigra (pars compacta) (*see* **Figs. 13.15 and 13.16**) in the midbrain, and just medially in the ventral tegmental area (VTA). Their axons project rostrally as the mesostriatal, mesolimbic, and mesocortical pathways to the cerebrum (meso for mesencephalon or midbrain).

The mesostriatal system from the substantia nigra to the striatum (caudate nucleus and putamen) of the basal ganglia is important in mechanisms of motor function (Chap. 24). Parkinson's disease is caused by a reduction or loss of inhibitory projections to the striatum following damage to the nigra (Chap. 24). The mesolimbic system from the VTA is connected to such limbic structures as the nucleus accumbens, amygdala, septal region, and ventral striatum (Chaps. 22 and 24). The mesocortical projections are from the VTA to frontal and cingulate gyri of the cortex (Chaps. 22 and 25). The latter two systems have been linked to schizophrenia (*dopamine hypothesis of schizophrenia*). It is thought that schizophrenia might be related to a relative excess in dopaminergic neuronal activity. Antipsychotic drugs that have therapeutic effects

are presumed to block dopamine receptors and, thus, reduce dopaminergic transmission.

Sensory Nerves, Their Ganglia, and Nuclei of Termination

The sensory cranial nerves and ganglia (equivalent to dorsal root ganglia) include the following: trigeminal nerve (n.V), trigeminal (Gasserian, semilunar) ganglion; facial nerve (n.VII), geniculate ganglion; vestibulocochlear (acoustic/vestibular) nerve (n.VIII), vestibular and spiral ganglia; glossopharyngeal nerve (n.IX), superior and inferior ganglia; and vagus nerve (n.X), also superior and inferior ganglia (*see* **Figs. 14.1 and 14.2**).

The brainstem nuclei of sensory cranial nerves are arranged in continuous columns (*see* **Fig. 14.2**) as follows:

1. *General somatic column* associated with cranial nerves V, VII, IX, and X. It comprises the *mesencephalic nucleus of n.V*, located lateral to the ventricular canal in the upper pons and midbrain (*see* **Fig. 13.13**), the *principal sensory nucleus of n.V*, located in the lateral tegmentum in the midpons (*see* **Fig. 13.13**), and the *spinal nucleus of n.V*, located laterally in the lower pontine tegmentum, medulla, and first two cervical spinal cord levels (*see* **Figs. 13.7 to 13.12**).
2. *Visceral column* associated with cranial nerves VII, IX, and X. This column, known as the *nucleus solitarius*, is located in the posterior tegmentum of the medulla (*see* **Figs. 13.9 to 13.11**).
3. *Special somatic column* associated with cranial nerve VIII. The four *vestibular nuclei* are located in the posterolateral tegmentum of the lower pons and upper medulla (*see* **Figs. 13.10 to 13.12**); the paired *cochlear nuclei* are located on the outer surface of the inferior cerebellar peduncle (*see* **Fig. 13.11**).

Motor Nerves and Their Nuclei of Origin Within the Brainstem

The brainstem nuclei of the motor cranial nerves are arranged in three discontinuous columns (*see* **Fig. 14.3**):

1. *General somatic column* associated with cranial nerves III, IV, VI, and XII. These motor nuclei are located in the posteromedial tegmentum. Those of nerves III and IV are in the midbrain (*see* **Figs. 13.14 to 13.16**), that of n.VI in the lower pons (*see* **Fig. 13.10**), and that of n.XII extends the length of the medulla (*see* **Figs. 13.9 and 13.10**).
2. *Special visceral column* consisting of three nuclei associated with cranial nerves V, VII, IX, X, and XI. The *motor nucleus of n.V* is located in the lateral tegmentum of the midpons (*see* **Fig. 13.13**), the *motor nucleus of n.VII* is in the caudal pontine tegmentum (*see* **Fig. 13.12**), and that of IX, X, and XI, known as the *nucleus ambiguus*, is within the central tegmentum throughout the medulla (*see* **Figs. 13.9 to 13.11**).
3. *General visceral (parasympathetic) column* emiting preganglionic fibers that are part of cranial nerves III, VII, IX, and X (*see* **Fig. 14.3**). The parasympathetic nucleus associated with n.III is the accessory nucleus of n.III (nucleus of Edinger–Westphal) in the midbrain (*see* **Fig. 13.14**); that associated with n.VII is the superior salivatory nucleus in the posterolateral tegmentum of the lower pons (*see* **Fig. 13.12**); that associated with n.IX is the inferior salivatory nucleus located in the posterior tegmentum of the rostral medulla (*see* **Fig. 13.11**); and that associated with n.X is the dorsal vagal nucleus located in the posterior tegmentum of the medulla (*see* **Figs. 13.9 and 13.10**).

TRANSVERSE SECTIONS THROUGH THE BRAINSTEM

In the following account, the anatomic relations of the intrinsic structures of the brainstem are briefly described in a representative series of transverse sections moving successively higher from the upper cervical spinal cord through the upper midbrain.

First Cervical Segment of the Spinal Cord (*see* Fig. 13.7)

The first cervical segment has several distinctive features. The fibers of the lateral corticospinal tract are located more medially than in the other spinal levels. Its location, abutting the gray matter, indicates that the tract has not completed its decussation. The myelinated fibers of the *spinal tract of n.V* and the large *spinal nucleus of n.V*, which extend to the C2 level, are the equivalents of the posterolateral tract and substantia gelatinosa of the spinal cord. The fibers of the *spinal root of cranial nerve XI* originate in the anterolateral aspect of the anterior horn and pass posteriorly and then laterally before emerging from the lateral side of the spinal cord. Although the dorsal root is absent at C1, the ventral root of the first cervical nerve is present.

Level of the Pyramidal Decussation (*see* Fig. 13.8)

This level is within the medulla. The most distinguishing feature is the crossing of 85–90% of the corticospinal tract fibers as the *pyramidal decussation*. It is composed of interdigitating descending fibers, which decussate and course in a caudal and posterior direction to the dorsal aspect of the lateral funiculus of the spinal cord. Dorsal spinal roots are absent. The spinal tract of n.V is composed of first-order fibers from cranial nerves V, VII, IX, and X, which descend as far as C2; they terminate throughout the length of the spinal nucleus of n.V (*see* **Fig. 9.6**). The fasciculus gracilis is smaller than the fasciculus cuneatus; both tracts are in the same location as in the spinal cord. The *nucleus gracilis* is present; it is the nucleus of termination for the fibers of the

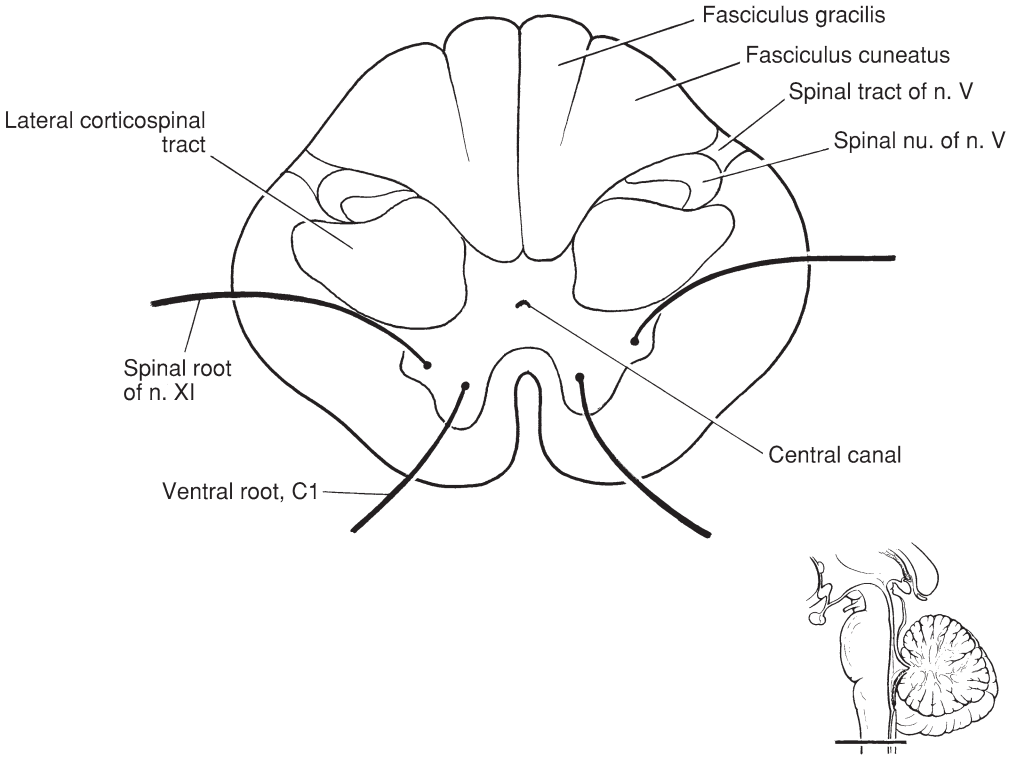


Figure 13.7: Transverse section of the upper portion of the first cervical segment.

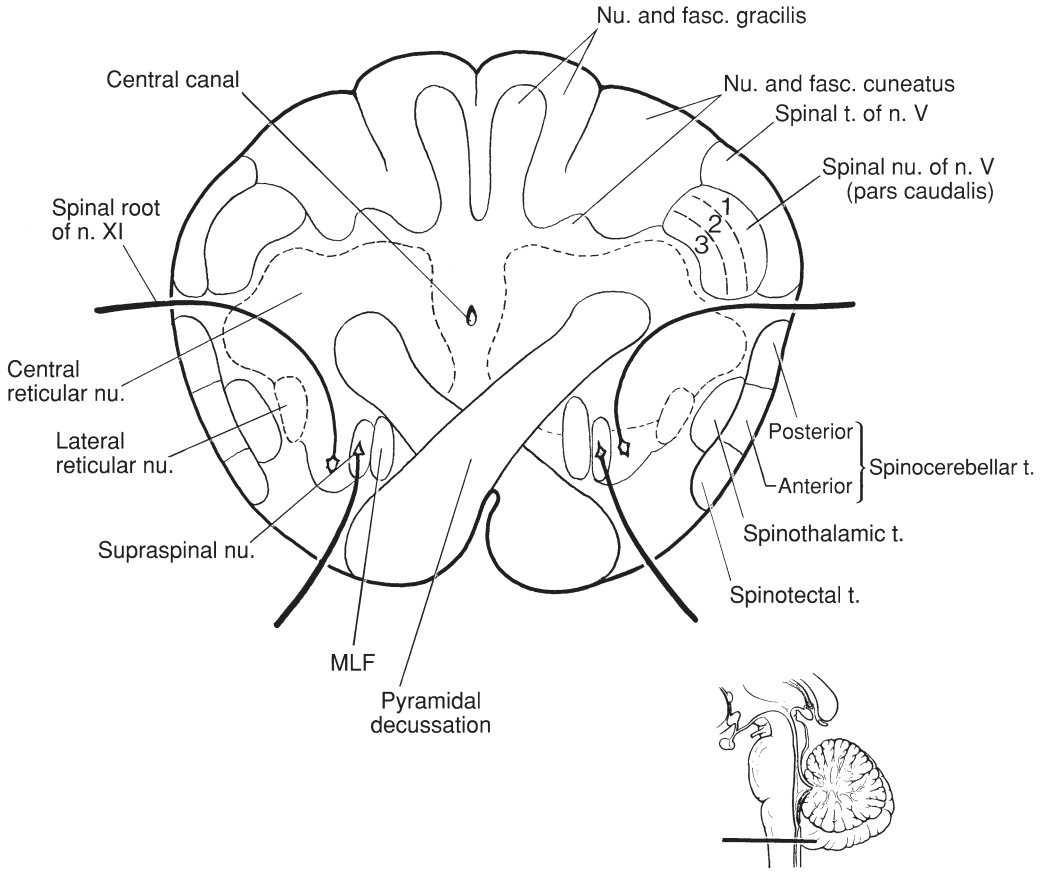


Figure 13.8: Transverse section of the lower medulla at the *level of the pyramidal (corticospinal) decussation*. The pars caudalis of the spinal trigeminal nucleus is called the posterior horn of the medulla because it is divisible into a (1) marginal lamina, (2) substantia gelatinosa, and (3) magnocellular layer.

fasciculus gracilis. The posterior and anterior spinocerebellar, spinothalamic, and spinotectal tracts have a relatively similar position to those in the spinal cord. The medial longitudinal fasciculus passes on the ventrolateral side of the decussating pyramidal fibers. The *central reticular nucleus* of the medulla occupies the bulk of the reticular formation from the spinal cord–medulla junction to the midolivary level. In the medial part of the ventral gray matter of the caudal medulla is a rostral extension of the anterior horn (lamina IX) of the spinal cord; this nucleus, which gives rise to ventral root fibers of the first cervical nerves, is called the *supraspinal nucleus*.

Level of Decussation of the Medial Lemniscus (*see* Fig. 13.9)

The distinguishing feature of this level is the curve of the *internal arcuate fibers*, which, after arising from cells in the enlarged nuclei gracilis and cuneatus, sweep anteriorly in an arc and decussate across the midline to form the medial lemniscus of the opposite side. Upon entering the medial lemniscus, these fibers bend and ascend rostrally through the

brainstem to the ventral posterolateral nucleus of the thalamus. The fasciculi gracilis and cuneatus are small because their fibers mainly have terminated within the corresponding nuclei. The *spinal tract* and *nucleus of the trigeminal nerve* are displaced anteriorly. Some of the fibers arising from this nucleus cross to the opposite side with the internal arcuate fibers and ascend to the thalamus as the *anterior trigeminothalamic tract* to terminate in the ventral posteromedial nucleus (*see* **Fig. 9.6**). They are second-order neurons, conveying pain and temperature information derived from the trigeminal nerve, nervus intermedius (VII), and glossopharyngeal and vagus nerves. In addition to the spinal nucleus of n.V, four other cranial nerve nuclei are present at this level. The *nucleus solitarius* (sensory, general visceral afferent [GVA], and special visceral afferent [SVA]), the *dorsal motor vagal nucleus* (parasympathetic, general visceral efferent [GVE]) and the *nucleus ambiguus* (motor, special visceral efferent [SVE]) all have components of the vagus nerve, which emerges through the dorsolateral sulcus of the medulla. The former two nuclei are located anterior to the nucleus gracilis and medial to the internal arcuate fibers; the nucleus ambiguus is located in the middle of the tegmentum just lateral to the internal arcuate fibers. Many of the fibers of the nucleus ambiguus from this level form the cranial root of the accessory nerve. The *hypoglossal nucleus* (general somatic efferent [GSE]), located anterior to the central canal on either side of the midline,gives rise to axons that pass downward through the medial tegmentum and emerge from the medulla between the pyramid and the olive (inferior olivary nuclear complex) at the preolivary sulcus.

The ascending tracts located in the lateral medulla (the posterior and anterior spinocere-

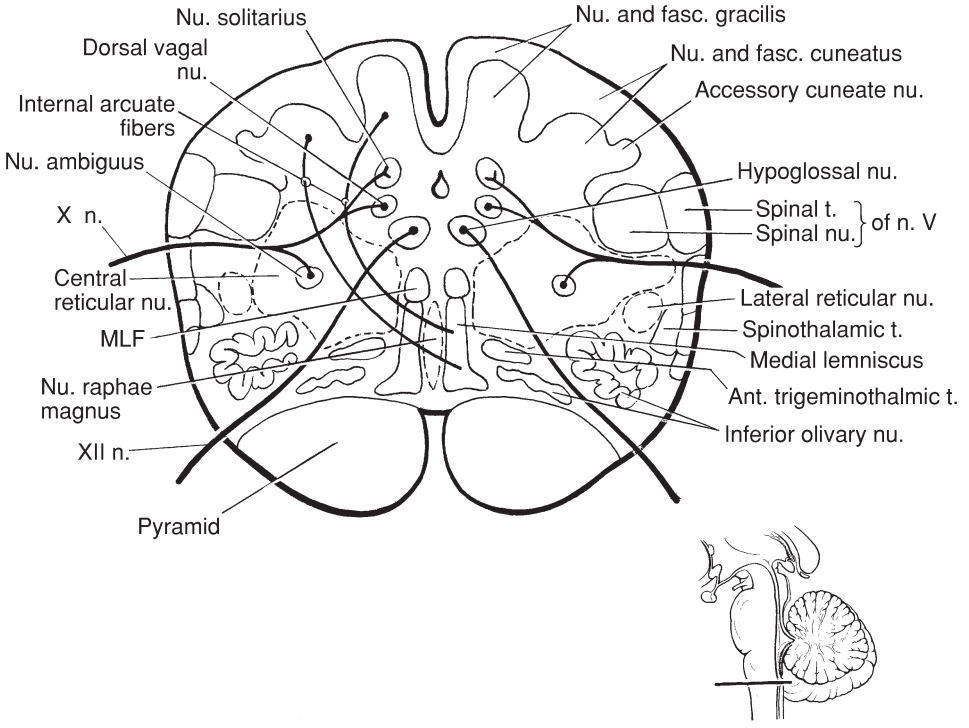


Figure 13.9: Transverse section of the lower medulla at the *level of the decussation of the medial lemniscus (internal arcuate fibers).*

bellar, spinothalamic, and spinotectal tracts) occupy the same general location as at more caudal levels.

Three prominent cerebellar relay nuclei of the medulla, referred to as *precerebellar nuclei*, are the source of fibers, which pass through the inferior cerebellar peduncle before terminating in the cerebellum. The first, the *accessory cuneate nucleus* of the lower medulla, located lateral to the cuneate nucleus, is the homolog of the dorsal nucleus of Clarke in the spinal cord; it receives proprioceptive input from the cervical and upper thoracic regions, especially the upper extremities, via uncrossed fibers ascending in the fasciculus cuneatus. The ipsilaterally projecting cuneocerebellar fibers from the accessory cuneate nucleus are the pathway from the upper extremity and are equivalent to the posterior spinocerebellar tract from the lower extremity. The second relay nucleus, the *lateral reticular nucleus*, is located in the vicinity of the spinothalamic tract at the level of the caudal two thirds of the inferior olivary nuclei. This nucleus receives afferent input from the spinal cord via spinoreticular and collateral branches of spinothalamic fibers and from fibers from the red nucleus of the midbrain. The third cerebellar relay group, the *inferior olivary complex*, is discussed in the next subsection.

Of the descending tracts and fibers, only the pyramids, composed of corticospinal fibers, are clearly demarcated. The anterior border of the medial longitudinal fasciculus (MLF) is not clearly defined because its fibers overlap with those of the medial lemniscus. At this level, the MLF is composed of (1) the pontine reticulospinal tract from the pars oralis and pars caudalis of the pontine reticular formation, (2) the interstitiospinal tract from the interstitial nucleus of Cajal in the midbrain, (3) the tectospinal tract from the midbrain tectum, and (4) vestibulospinal fibers from the medial vestibular nucleus.

Just posterior to the inferior olivary nuclear complex, within the reticular formation, are fibers of the rubrospinal tract from the red nucleus in the midbrain, the medullary reticulospinal tract from the nucleus reticularis gigantocellularis of the medulla, and the vestibulospinal tract from the lateral vestibular nucleus. The fibers of these tracts are intermingled with other fibers; hence, they are not clearly delineated.

The *reticular nuclei* include the nucleus raphe magnus, central reticular nucleus, and lateral reticular nucleus; these belong to the raphe, central, and lateral nuclear groups, respectively. Just rostral to this level is the obex (*see* **Fig. 13.2**), located at the most caudal end of the fourth ventricle.

Level of the Middle Third of the Inferior Olivary Complex (*see* Fig. 13.10)

The distinguishing features of this level are the nuclei of the inferior olivary complex, fourth ventricle, inferior cerebellar peduncle, and cranial nerve nuclei. The *olivary complex* comprises the phylogenetically new *principal inferior olivary nucleus* together with phylogenetically old *dorsal* and *medial accessory olivary nuclei*. Efferent fibers from the inferior olivary complex decussate and pass successively through the medial lemnisci, the vicinity of the contralateral olivary complex, and the inferior cerebellar peduncle before terminating in the cerebellum. The accessory olivary nuclei project primarily to the vermis of the cerebellum, whereas fibers from the principal olivary nucleus terminate in the contralateral cerebellar hemisphere. Olivocerebellar fibers carry excitatory input to the deep cerebellar nuclei and the entire cerebellar cortex. The input to the inferior olivary nuclei is derived from the spinal cord, cerebral cortex, red nucleus, periaqueductal gray of the midbrain, and the deep cerebellar nuclei. The spinoolivary fibers ascend in the anterior funiculus. Originating from the frontal, parietal, temporal, and occipital lobes, corticoolivary fibers descend with the corticospinal tract before terminating bilaterally. Fibers from the red nucleus and periaqueductal gray descend in the central tegmental tract. Some of the fibers from the deep cerebellar nuclei, after emerging from the cerebellum via the superior cerebellar peduncle,

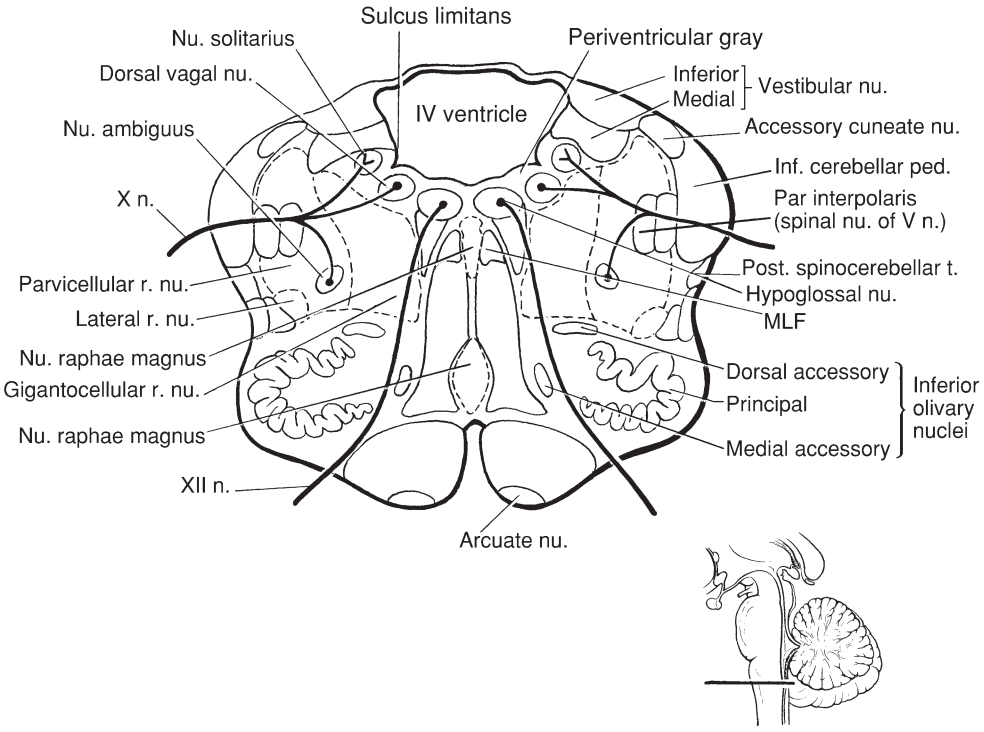


Figure 13.10: Transverse section of the medulla at the *level of the middle of the inferior olive*. The arcuate nuclei are minor nuclei projecting to the cerebellum.

decussate in the lower midbrain and descend in the central tegmental tract to the inferior olivary complex.

In the tegmentum anterior to the floor of the fourth ventricle is a row of cranial nerve nuclei. Two motor nuclei, located medial to the fovea (sulcus limitans), are the hypoglossal general somatic efferent (GSE) and dorsal vagal general visceral efferent (GVE) nuclei. Two sensory nuclear groups, located laterally to the fovea, are the nucleus solitarius (GVA and SVA) and the medial and inferior vestibular special somatic afferent (SSA) nuclei. The nucleus ambiguus special visceral efferent (SVE) is a motor nucleus located in the middle of the tegmentum. The spinal nucleus of n.V is a sensory nucleus in the dorsolateral tegmentum. The vagus nerve is associated with the nucleus ambiguus, dorsal vagal nucleus, nucleus solitarius, and the spinal nucleus of n.V.

The *paramedian reticular nuclei* (nuclei lateral to medial lemniscus in vicinity of inferior olivary nucleus) and the nearby *arcuate nucleus* relay influences via the inferior cerebellar peduncles to the cerebellum. The cells of the *raphe nuclei (nucleus raphe magnus)* contain serotonin (5-hydroxytryptamine) and project to the spinal cord.

The *central reticular nuclear group* at upper medullary levels consists of the *gigantocellular reticular nucleus*, which is located posterior to the inferior olivary complex. This large-celled nucleus occupies the medial two-thirds of the reticular formation as far rostral as the medullary–pontine junction. Input to this nucleus is derived largely from (1) widespread areas of the cerebral cortex via crossed and uncrossed corticoreticular fibers, (2) higher brainstem levels via the central tegmental tract, (3) neurons from the parvicellular nucleus of

the lateral nuclear group, and (4) spinoreticular fibers ascending in the anterolateral funiculus of the spinal cord. The output from the gigantocellular reticular nucleus projects (1) rostrally via the central tegmental tract to higher brainstem levels and to the intralaminar nuclei of the thalamus and via the median forebrain bundle to the hypothalamus and (2) caudally via the medullary (lateral) reticulospinal tract to the spinal cord.

The *lateral reticular zone* consists of the *lateral reticular nucleus* and *parvicellular reticular nucleus*. Input to the parvicellular reticular nucleus is derived from (1) widespread areas of the cerebral cortex via crossed and uncrossed corticoreticular fibers, (2) collateral fibers from the auditory, vestibular, trigeminal, and visceral pathways, and (3) spinoreticular fibers from the spinal cord. The output from the parvicellular reticular nucleus is directed medially to the gigantocellular reticular nucleus. Except for possible minor changes, the locations of the ascending and descending tracts and pathways are similar to those described in the Level of Decussation of the Medial Lemniscus subsection. The posterior spinocerebellar tract is close to the inferior cerebellar peduncle, which it is about to join.

Tangential Section at the Levels of the Glossopharyngeal and Vestibulocochlear Nerves (*see* Fig. 13.11)

This medullary level is in the vicinity of the medullopontine junction. It is different from the midolivary level in several respects. Among these are the absence of the hypoglossal and dorsal vagal nuclei, the presence of cranial nerve nuclei associated with the glossopharyngeal, cochlear, and vestibular nerves, and the presence of the inferior cerebellar peduncle, which can be seen extending from the medulla into the cerebellum.

The nuclei associated with the glossopharyngeal nerve include the nucleus solitarius, spinal nucleus of n.V, inferior salivatory nucleus, and nucleus ambiguus. These nuclei are discussed in Chapter 14.

The dorsal and ventral cochlear nuclei are situated on the outer surface of the inferior cerebellar peduncle. Fibers of the cochlear nerve branch in an organized sequence so that each fiber is distributed in a precise pattern to both the dorsal and ventral cochlear nuclei. At a slightly higher level (right side of **Fig. 13.11**), fibers of the vestibular nerve pass at right angles among the fibers of the inferior cerebellar peduncle enroute to the four vestibular nuclei (medial, inferior, and lateral vestibular nuclei are illustrated).

In **Fig. 13.11**, the large inferior cerebellar peduncle (left side) is illustrated as it passes (right side) into the cerebellum. The peduncle contains the following fibers passing to the cerebellum: posterior spinocerebellar, cuneocerebellar, and olivocerebellar tracts, along with fibers from such nuclei as the lateral reticular and paramedian reticular nuclei. A portion of the inferior cerebellar peduncle, called the *juxtarestiform body*, is composed of fibers associated with the vestibular system conveying influences to and from the vestibulocerebellum and the fastigial nuclei of the cerebellum.

The reticular nuclei at this level include the raphe magnus, gigantocellularis and parvicellularis.

The four deep cerebellar nuclei, oriented in order from medial to lateral, are the fastigial, globose, emboliform, and dentate nuclei. The globose and emboliform nuclei are collectively called the *nucleus interpositus*. The fibers of the inferior cerebellar peduncle pass lateral to the dentate nucleus. The juxtarestiform body is located between the deep cerebellar nuclei and the lateral border of the fourth ventricle.

Level of Nuclei of Sixth and Seventh Cranial Nerves (*see* Fig. 13.12)

The general pattern of organization at this level differs from that of the levels of the medulla primarily because of the massive size of the ventral or basilar pons relative to the dorsal or tegmental pons. The *ventral pons* represents a modified, rostral continuation of the pyramids of the medulla. The *tegmentum of the pons* represents a rostral continuation of the medulla exclusive of the pyramids. The boundary between the dorsal and ventral pons is a

plane located just anterior to the medial lemniscus. The fourth ventricle is large.

The *basilar pons* consists of the corticospinal tract, pontine nuclei, terminal branches of the descending corticopontine fibers to the pontine nuclei, and pontocerebellar fibers; the latter pass from the pontine nuclei through the middle cerebellar peduncle to the cerebellum.

Except for a few significant modifications, the dorsal pons resembles the medulla. The MLF is still located anterior to the fourth ventricle and just lateral to the midline, whereas the spinal tract and nucleus of the trigeminal nerve are in the dorsolateral tegmentum. However, the medial lemniscus has shifted from a ventromedial tegmental location (vertical

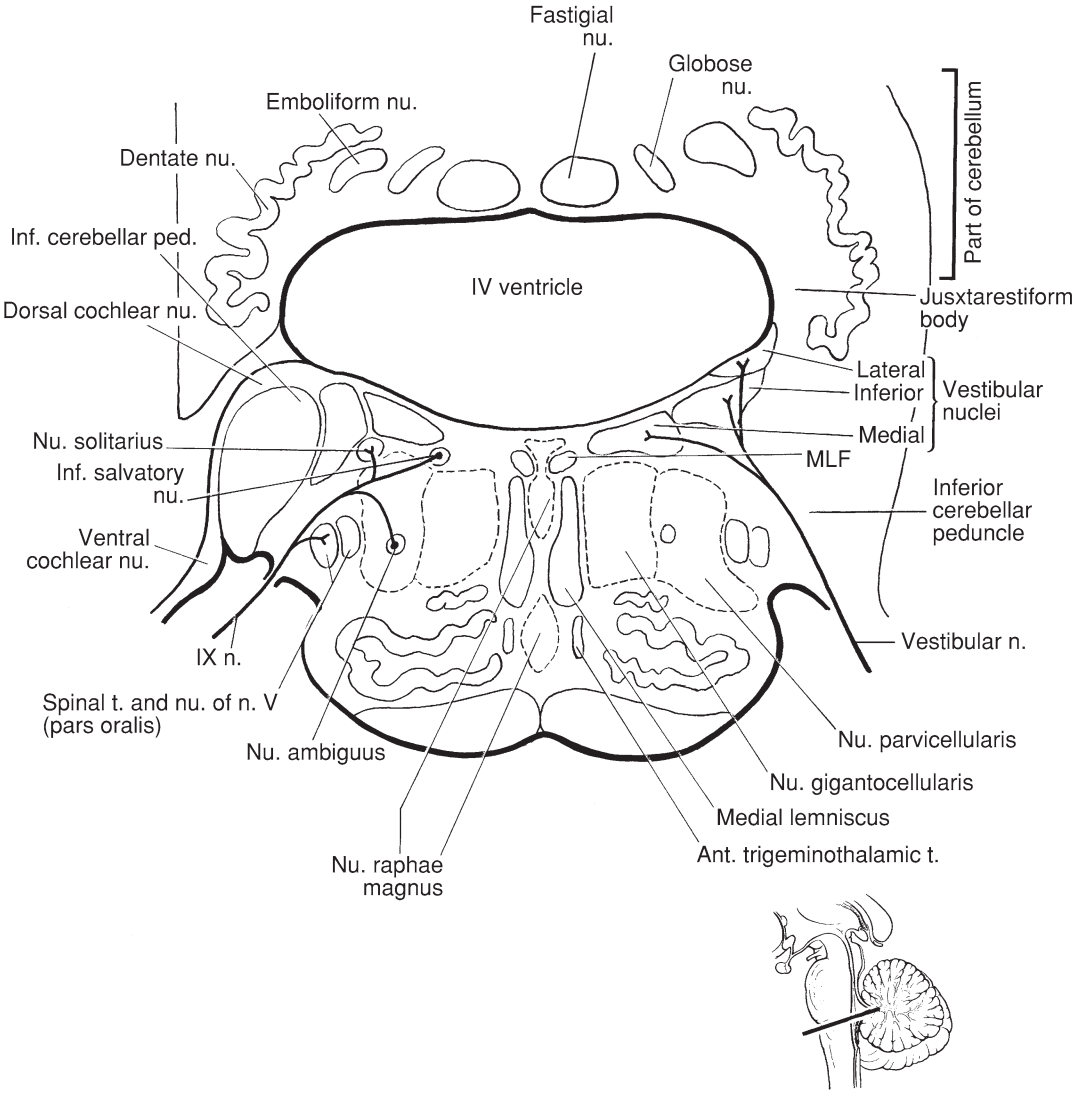


Figure 13.11: Transverse section (slightly oblique) of the upper medulla at the *level of the cochlear and glossopharyngeal nerves (left) and the vestibular nerve (right)*. Section includes the cerebellum and its deep cerebellar nuclei.

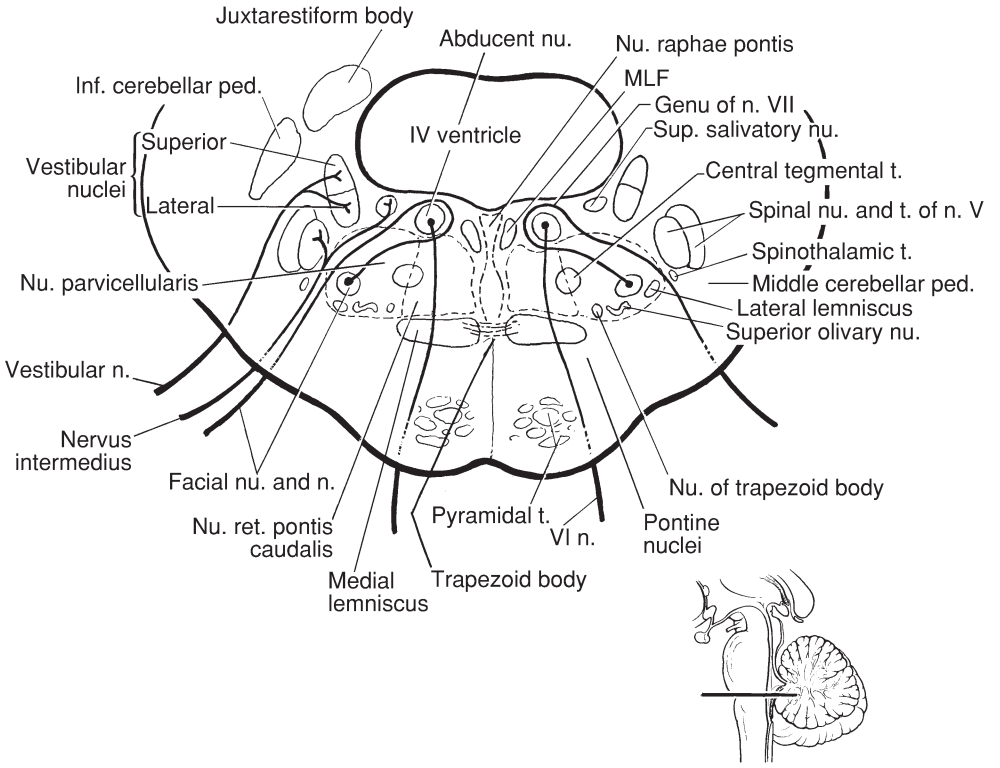


Figure 13.12: Transverse section of the lower pons at the *level of the sixth and seventh cranial nerves*.

orientation) in the medulla to a ventral tegmental location (horizontal orientation) in the pons. The central tegmental tract is prominent in the middle of the reticular formation.

The cranial nerve nuclei present at this level have their equivalents in the medulla. The *abducent nucleus, motor nucleus of the facial nerve,* and the *superior salivatory nucleus* are located within the tegmentum in sites similar to those occupied within the medulla by the hypoglossal nucleus, nucleus ambiguus, and dorsal vagal nucleus, respectively. The *superior vestibular nucleus* is found in the posterolateral tegmentum. The course of the fibers of the abducent and facial nerves is characteristic and significant. The lower motoneurons of the sixth nerve emerge from the abducent nucleus and pass ventrally through the medial tegmentum and basal pons lateral to the pyramidal tract before emerging medially at the pontomedullary junction. After emerging from the facial nucleus, the lower motoneurons form a bundle that follows a circuitous course. The facial nerve passes posteromedially, ascends for a short distance medial to the abducent nucleus, and then, as the *genu of n.VII*, passes posterior to the abducent nucleus; finally, it turns laterally before continuing anterolaterally through the lateral tegmentum before emerging from the brainstem at the cerebellopontine angle (*see* **Fig. 13.3**). The hillock in the floor of the fourth ventricle at the site of the abducent nucleus and the internal genu is called the *facial* or *abducent colliculus*. The nervus intermedius is a part of n.VII (Chap. 14); some of its fibers originate in the superior salivatory nucleus and others terminate in the spinal nucleus of n.V and the nucleus solitarius.

The superior and inferior salivatory nuclei are diffuse and confluent groups of cells located within and close to the parvicellular reticular nucleus (*see* **Figs. 13.11 and 13.12**). Components of the auditory pathways found at this level are the *superior olivary complex* and the *lateral lemniscus*, which is located in the ventrolateral tegmentum. Auditory fibers decussating between the olives constitute the trapezoid body (*see* **Figs. 13.12 and 16.6**).

The reticular nuclei at this level and those of the lower pons caudal to the principal nucleus of the trigeminal nerve are the *nucleus raphe pontis* (a raphe nucleus), the *nucleus reticularis pontis caudalis* (a central reticular group nucleus), and the *nucleus parvicellularis* (a lateral reticular nucleus).

Level of the Trigeminal Nerve (*see* Fig. 13.13)

The characteristic features at this midpontine level are (1) the *principal sensory nucleus* and *motor nucleus of the trigeminal nerve* and (2) the *superior cerebellar peduncle* on the lateral aspect of the narrowing fourth ventricle.

The *principal nucleus of n.V* is a nucleus of termination of the sensory root of the trigeminal nerve; other fibers of this root have their cell bodies in the *mesencephalic nucleus of n.V*, which is located lateral to the fourth ventricle. The *motor nucleus of n.V*, located medial to the principal nucleus, contains the cell bodies of the lower motoneurons that form the motor root of the trigeminal nerve.

The *superior cerebellar peduncle* is primarily composed of cerebellar efferent fibers orig-

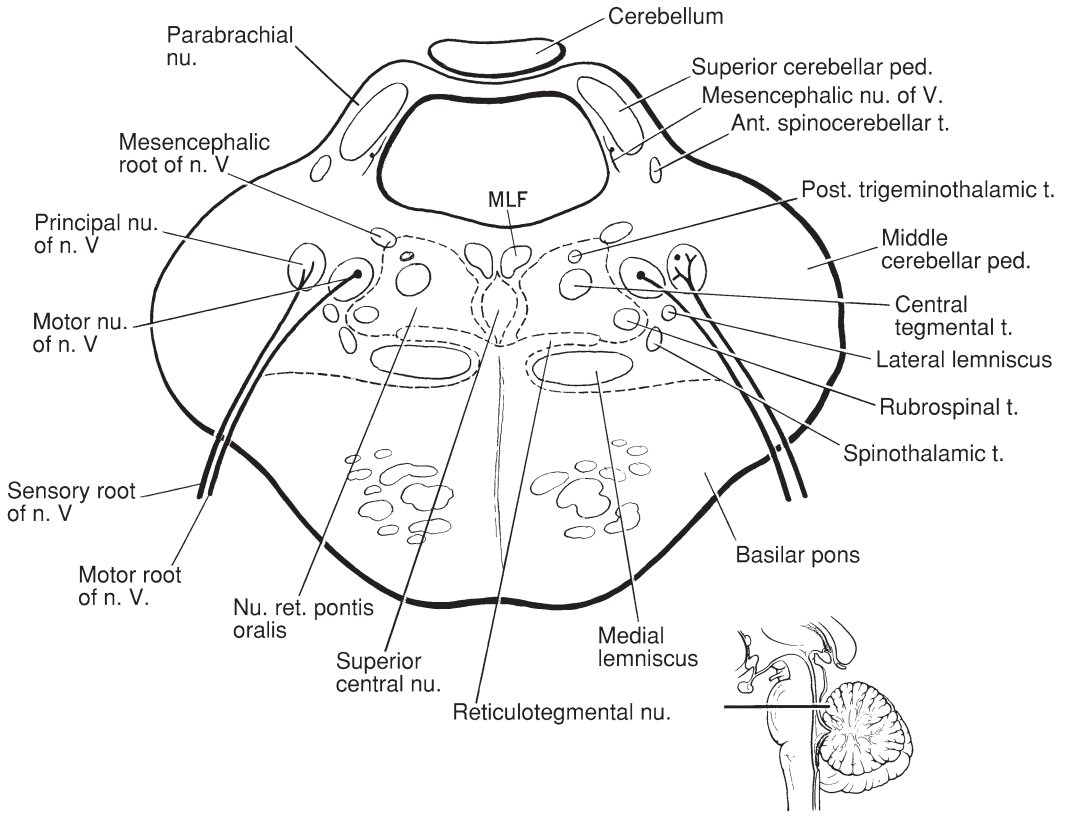


Figure 13.13: Transverse section of the midpons at the *level of the entrance of the trigeminal nerve*.

inating in the dentate, emboliform, and globose nuclei; these fibers decussate in the lower midbrain tegmentum and (1) ascend to the nucleus ruber and to the rostral intralaminar and ventrolateral thalamic nuclei and (2) descend in the brainstem tegmentum to the reticulotegmental nucleus of the pons and the inferior olivary and paramedian nuclei of the medulla. The anterior spinocerebellar tract courses posteriorly in the superior cerebellar peduncle; its fibers terminate in the anterior vermal cortex.

The medial lemniscus has shifted somewhat laterally and the spinothalamic tract and lateral lemniscus have shifted slightly dorsolaterally along the outer margin of the reticular formation. The medial longitudinal fasciculus, central tegmental tract, rubrospinal tract, and the structures of the basilar pons have the same topographic relations to one another as those described in the previous section. The lateral lemniscus contains a small diffuse aggregation of neurons called the nucleus of the lateral lemniscus.

The reticular nuclei extending from this level up to the lower midbrain are (1) the *superior central nucleus* (a raphe nucleus), (2) the *reticulotegmental nucleus* (actually an extension of the pontine nucleus of the basilar pons into the tegmentum [as do the pontine nuclei, the reticulotegmental nucleus projects its fibers to the cerebellum]), and (3) the *nucleus reticularis pontis oralis* and *locus ceruleus* (*see* **Fig. 13.14**) (central reticular nuclei). The cells of the locus ceruleus are noradrenergic neurons whose axons are distributed to the (1) cerebellum, (2) cerebrum, including directly to the cerebral cortex, (3) brainstem, and (4) spinal cord.

Level of the Inferior Colliculus (*see* Fig. 13.14)

The distinguishing features at this level include the inferior colliculi and the decussation of the superior cerebellar peduncle. The ventricular system is represented by the narrow *cerebral aqueduct*.

The large *nucleus of the inferior colliculus* is a major processing station in the auditory pathways. It receives input from ascending auditory fibers of the lateral lemniscus and from descending fibers from the medial geniculate body; it projects influences (1) rostrally to the medial geniculate body via the brachium of the inferior colliculus and to the superior colliculus and (2) caudally to auditory nuclei via the lateral lemniscus. The bilateral nuclei of the inferior colliculi are interconnected by fibers in the commissure of the inferior colliculus. As a group, the medial lemniscus, spinothalamic tract, and lateral lemniscus have shifted laterally and dorsally along the outer margin of the reticular formation of the tegmentum. In this shift, the lateral lemniscus approaches the inferior colliculus; its fibers enter and terminate in the nucleus of the inferior colliculus. The rostrally projecting fibers from the latter form the brachium of the inferior colliculus, which is located in the dorsolateral tegmentum of the upper midbrain.

The *posterior trigeminothalamic tract,* from the ipsilateral principal nucleus of n.V, is located in the tegmentum posterior to the central tegmental tract. The anterior trigeminothalamic tract, from the contralateral spinal and principal nuclei of n.V, is located between the medial lemniscus and spinothalamic tract. The MLF is notched posteriorly by the nucleus of the trochlear nerve. The fibers of the trochlear nerve (IV) pass as a dorsocaudally directed arc from this nucleus along the outer edge of the periaqueductal gray matter; they decussate completely in the superior medullary velum and emerge from the posterior tectum caudal to the inferior colliculus. The locus ceruleus is located deep to the inferior colliculus.

The reticular nuclei at this level include (1) the *dorsal* and *ventral raphe tegmental nuclei* (raphe nuclei), (2) the rostral portion of the *nucleus reticularis pontis oralis* and *locus ceruleus* (central reticular nuclei), and (3) *pedunculopontine* and *cuneiform nuclei* (lateral reticular group nuclei). The dorsal tegmental nucleus (supratrochlear nucleus) is located dorsal to the trochlear nucleus in the periaqueductal gray matter; it receives input from the mammillary body. The ventral tegmental nucleus is present ventral to the

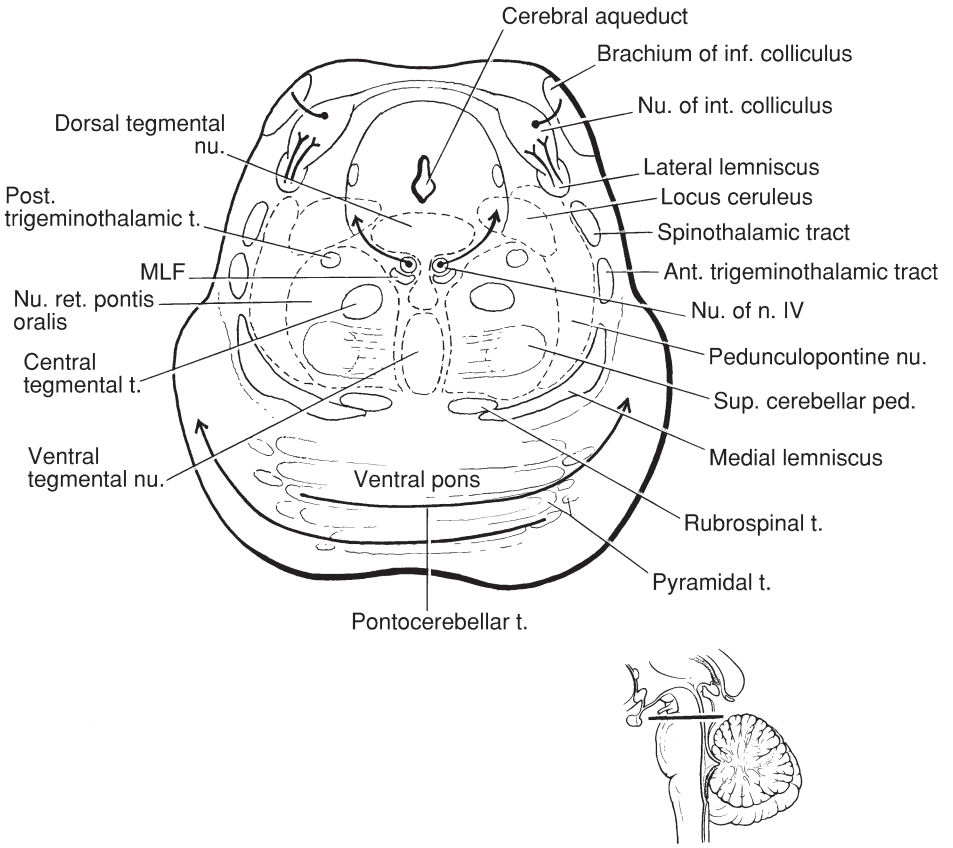


Figure 13.14: Transverse section of the lower midbrain at the *level of the inferior colliculus and nucleus of the fourth cranial nerve*.

medial longitudinal fasciculus; it is apparently a rostral extension of the superior central nucleus. The pedunculopontine nucleus lies in the caudal midbrain lateral to the superior cerebellar peduncle and medial to the medial lemniscus. It is the only brainstem nucleus that receives direct input from the globus pallidus (*see* **Fig. 24.3**).

Section Through Midbrain at Level of Superior Colliculus (*see* Fig. 13.15)

The major characteristic features at this level are the *superior colliculus, nucleus of the oculomotor nerve, red nucleus, substantia nigra,* and *crus cerebri*. The medial geniculate body, marking the most caudal nucleus of the diencephalon (or thalamus), is present.

The laminated superior colliculus and the rostrally located pretectum (*see* **Fig. 13.16**) are reflex centers. The superficial layers of the superior colliculus receive direct input from the retina and the visual cortex. The deep layers receive inputs from the auditory and somatosensory systems. The superior colliculus has roles in orienting the head and eyes toward a visual stimulus. The pretectum is part of the circuitry involved in the direct and consensual light reflexes (Chap. 19).

The *red nucleus* is a large oval nucleus in the medial tegmentum. It is composed of a caudal magnocellular part and a rostral parvicellular part. Some fibers of the superior cerebellar peduncle terminate within the nucleus, whereas others pass through it and along its outer

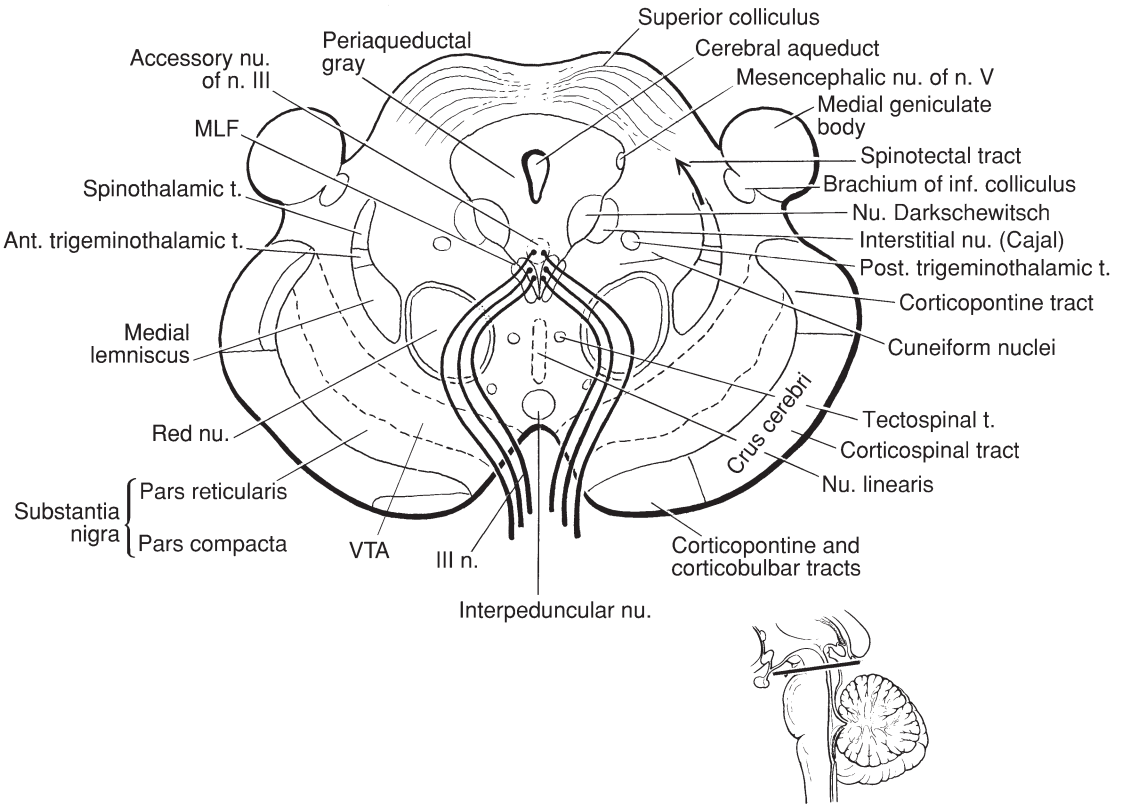


Figure 13.15: Transverse section of the upper midbrain at the *level of the superior colliculus and the third cranial nerve*. The medial region between the bilateral substantia nigra is called the ventral tegmental area (VTA). The VTA contains dopaminergic neurons that project rostrally to the forebrain, including the nucleus accumbens, a component of the limbic system (Chap. 22).

margins as a "capsule," on their way to the ventral lateral, ventral anterior, and some intralaminar thalamic nuclei.

The rubrospinal tract originates from cells in the caudal one-fourth of the red nucleus; its fibers cross as the ventral tegmental decussation before descending as the rubrospinal tract in the anterior tegmentum.

The *oculomotor nuclear complex* is located in a V-shaped region formed by the paired medial longitudinal fasciculi. The fibers of the oculomotor nerve (III) arise in this nucleus and course anteriorly through the medial tegmentum, including the red nucleus, on their way to emerge as rootlets from the interpeduncular fossa.

The *substantia nigra* is located between the tegmentum and the crus cerebri. It is divided into a pars compacta and a pars reticularis. The large cells of the compact (or black) part contain melanin pigment and primary catecholamines; these cells synthesize and convey dopamine, via nigrostriatal fibers, to the neostriatum (caudate nucleus and putamen). The cells of the reddish brown pars reticularis contain iron, but no melanin pigment.

The *crus cerebri* is the basilar part of the midbrain. It is composed of descending corticofugal fibers, which originate in the cerebral cortex. The corticospinal and corticobulbar fibers are located in the middle two-thirds (*see* **Fig. 13.15**). They are said to be somatotopi-

cally organized at this level with the head andupper-extremity and lower-extremity musculature influenced by nerve fibers arranged from medial to lateral within the crus. Frontopontine fibers are located in the medial portion, and corticopontine fibers from the parietal, temporal, and occipital cortical areas are in the lateral portion of the crus. The most medial and lateral portions of the crus may contain some corticobulbar fibers.

The medial lemniscus, anterior trigeminothalamic tract, and spinothalamic tract have shifted to a slightly more dorsal location in the tegmentum. The brachium of the inferior colliculus (auditory tract) is located dorsolateral to the spinothalamic tract; it is heading to the medial geniculate body. The posterior trigeminothalamic tract is located in the dorsomedial tegmentum. The interpeduncular nucleus is located at the midline just dorsal to the interpeduncular fossa. Dorsal to this nucleus is the ventral tegmental area (VTA, not labeled) (Chap. 15). Neurons of VTA have been implicated with the reward properties of cocaine addiction (Chap. 22).

Reticular nuclei at this level include nuclei linearis (raphe nuclei), *nucleus ruber*, which is considered to be a specialized central reticular nucleus, and *cuneiform nuclei* (lateral reticular nuclear group). Nonreticular nuclei include the *interpeduncular nucleus, mesencephalic nucleus of the trigeminal nerve, interstitial nucleus of Cajal,* and the *nucleus of Darkschewitsch*.

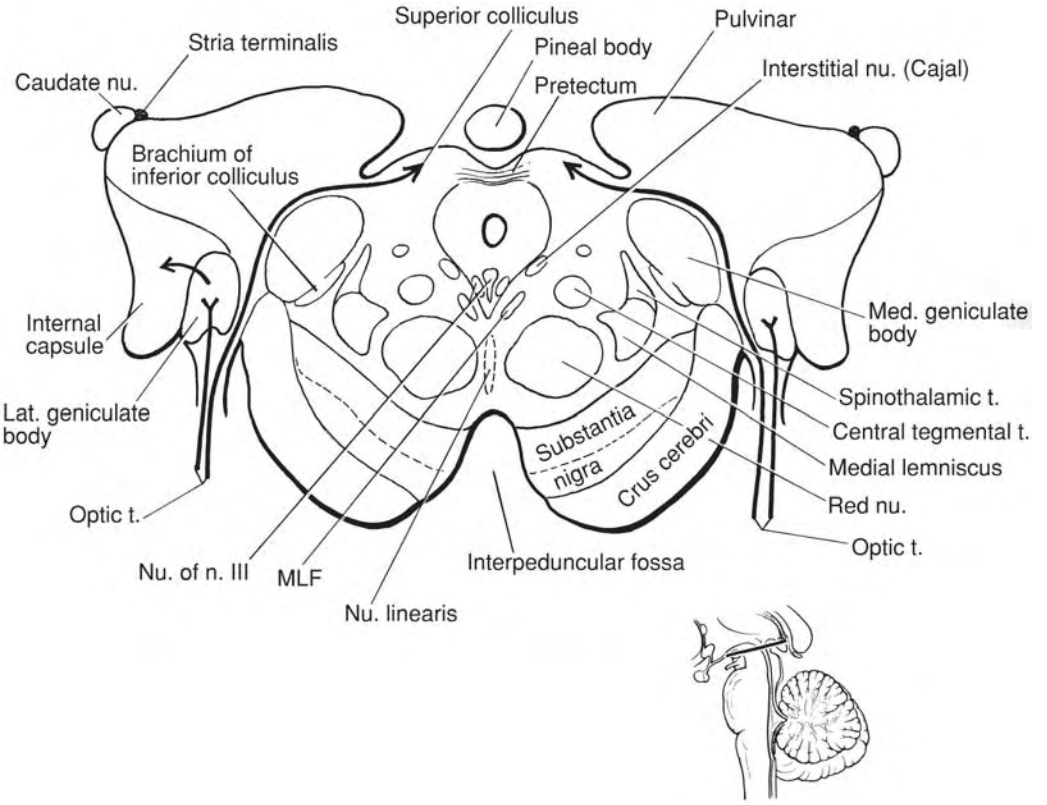


Figure 13.16: Transverse section at the junction of the upper midbrain and diencephalon.

Transverse Section Through Junction of Midbrain and Thalamus (*see* Fig. 13.16)

In this section are structures of the upper midbrain and the adjoining cerebrum. The midbrain is only slightly changed from the previous section (**Fig. 13.15**). The pulvinar and medial and lateral geniculate bodies belong to the thalamus (Chap. 23). Also illustrated are the caudate nucleus (a basal ganglion, Chap. 24), stria terminalis (a tract of the limbic system, Chap. 22), internal capsule (fibers of the cerebrum; Chap. 23), and pineal body (Chap. 22).

The brachium of the inferior colliculus (auditory pathways) terminates in the medial geniculate body of the thalamus. Note that the fibers in the optic tract end either in the lateral geniculate body of the thalamus or in the superior colliculus and pretectum (Chap. 19). The ascending reticular pathway fibers of the central tegmental tract terminate in the intralaminar nuclei of the thalamus (*see* **Fig. 22.1**).

Refer to the previous section for a discussion of the superior colliculus, pretectum (pretectal area), oculomotor nerve (n.III), substantia nigra, and crus cerebri.

SUGGESTED READINGS

Brodal A. *The Reticular Formation of the Brain Stem; Anatomical Aspects and Functional Correlations.* Henderson Trust Lectures, No. 18. Edinburgh: Oliver and Boyd; 1957.

DeMyer W. *Neuroanatomy.* Malvern, PA: Harwal; 1998, p. 170.

Felten DL, Sladek JR, Jr. Monoamine distribution in primate brain V. Monoaminergic nuclei: anatomy, pathways and local organization. *Brain Res. Bull.* 1983;10:171–284.

Garver DL, Sladek JR Jr. Monoamine distribution in primate brain. I Catecholamine-containing perikarya in the brain stem of Macaca speciosa. *J Comp. Neurol.* 1975;159:289–304.

Garver DL, Sladek JR Jr. Monamine distribution in primate brain. II. Brain stem catecholaminergic pathways in Macaca speciosa (arctoides). *Brain Res.* 1976;103:176–182.

Hobson JA, Brazier MAB, eds. *The Reticular Formation Revisited: Specifying Function for a Nonspecific System.* New York: Raven; 1980.

Olszewski J, Baxter D. *Cytoarchitecture of the Human Brain Stem.* 2nd ed. New York: Karger; 1982.

Peterson BB. The reticulospinal system and its role in the control of movement. In: Barnes C, ed. *Brainstem Control of Spinal Cord Function.* New York: Academic; 1984.

14
Cranial Nerves and Chemical Senses

Classification of Cranial Nerves
Ganglia in the Head
Cranial Nerve Nuclei Within the Brainstem
Some Functional and Clinical Considerations
Chemical Senses (Olfaction and Gustation)

Twelve pairs of cranial nerves are peripheral nerves of the brain (*see* **Fig. 14.1**). The olfactory and optic nerves are nerves of the cerebrum (telencephalon). The other 10 pairs are nerves of the brainstem (and in one case, partially of the cervical spinal cord). They supply structures of the head and neck and, in the case of the vagus nerve, structures of the trunk. Some cranial nerves contain almost exclusively afferent fibers, others almost exclusively efferent fibers, and a third group contains substantial proportions of both afferent and efferent fibers (*see* **Table 14.1**). The afferent fibers arise with one exception, those that mediate unconscious proprioception, from cell bodies located in peripheral ganglia; their central processes enter the brainstem and end in sensory nuclei of termination (*see* **Fig. 14.2**). Efferent fibers arise from cell bodies located in brainstem motor nuclei (*see* **Fig. 14.3**). Cranial nerves pass to and from the cranial cavity through foramina, canals, and fissures in the skull.

CLASSIFICATION OF CRANIAL NERVES

Many of the cranial nerves have the same general functional components as occur in spinal nerves: general somatic afferent (GSA), general visceral afferent (GVA), general somatic efferent (GSE), and general visceral efferent (GVE). In addition, many cranial nerves have special components: special somatic afferent (SSA), special visceral afferent (SVA), and special visceral (branchial) efferent (SVE). The terms defining the components are used as follows: *somatic* refers to head, body wall, and extremities; *visceral* refers to viscera; *afferent* refers to sensory (input); *efferent* refers to motor (output); *general* refers to wide areas of the head and body; *special* refers to the specialized functions of olfaction (smell), gustation (taste), vision, audition, equilibrium (vestibular system), and branchiomeric (gill arch) muscles. Cranial nerves are classified into one of three groups, depending on the main function component: special afferent, general efferent, and branchiomeric or mixed (*see* **Table 14.1**).

Special Afferent Nerves

These sensory nerves serve the special senses (i.e., smell, sight, hearing, and balance [equilibrium]). Included are two special *somatic* afferent (SSA) nerves:

Optic (II)
Vestibulocochlear (VIII) and a special visceral afferent (SVA) nerve
Olfactory (I)

Taste, also SVA, is mediated by components of three branchiomeric nerves: cranial nerves VII, IX, and X.

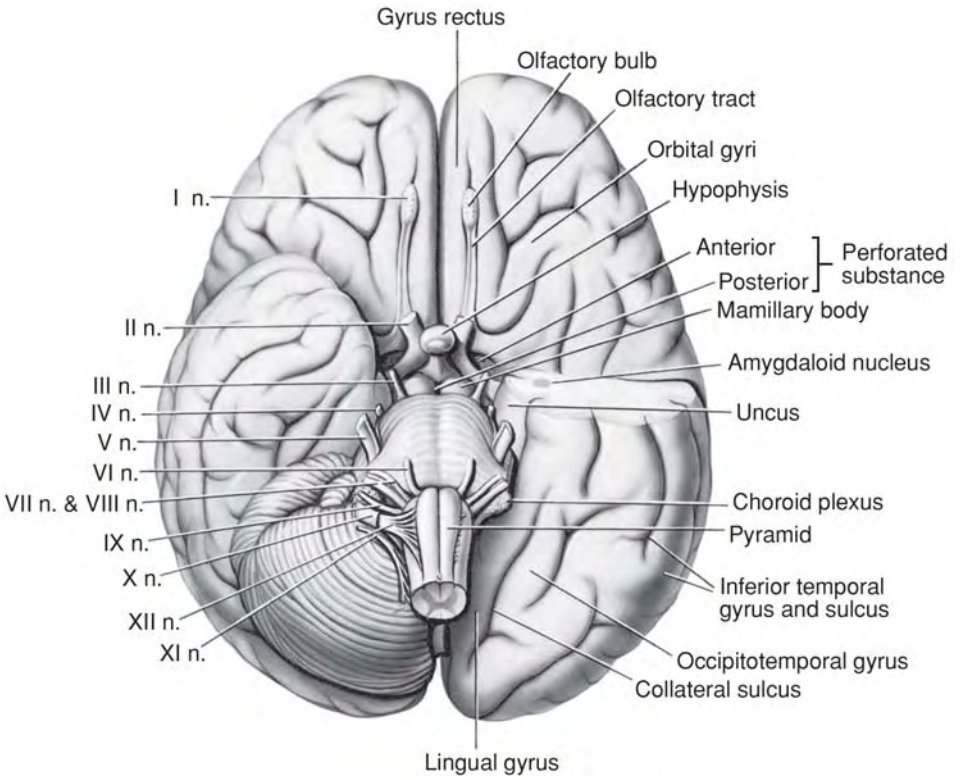


Figure 14.1: Basal surface of the brain and roots of the cranial nerves. The cerebellum and rostral portion of the temporal lobe are removed on the right side of the figure to better show nerves located at the cerebellopontine angle and some unrelated components of the cerebrum.

General Somatic Efferent Nerves

These are motor nerves that supply voluntary muscles derived from embryonic somites, specifically skeletal muscles, except branchiomeric ones:

Oculomotor (III)
Trochlear (IV)
Abducent (VI)
Hypoglossal (XII)

They innervate the voluntary somatic muscles of the eye and tongue. In addition to GSE fibers, the oculomotor nerve contains parasympathetic (GVE) fibers to the involuntary muscles of the eye (Chap. 19).

Branchiomeric (Visceral) Nerves

The nerves in this category are mixed (both afferent and efferent) in function.

It includes motor components that innervate branchiomeric muscles (i.e., striated muscles that arise from branchial arches of the embryo). (Branchial arches are a series of elevations, separated by clefts, on the walls of the primitive pharynx. The clefts are so clearly homologous to those found in lower vertebrates such as fish that they are believed to be phylogenetically related to gills. In embryonic development, muscle-forming cells called *myoblasts* congregate in the branchial arches, where they give rise to much of the head and neck musculature.) The fibers

Table 14-1: Cranial Nerves and Their Functional Components

Name	*Components*	*Functions (major)*
I. Olfactory nerve	Special visceral afferent	Smell
II. Optic nerve	Special somatic afferent	Vision
III. Oculomotor nerve[a]	General somatic efferent	Movement of eyes
	General visceral efferent (parasympathetic)	Pupillary constriction and accommodation
IV. Trochlear nerve[a]	General somatic efferent	Movements of eyes
V. Trigeminal nerve	Special visceral efferent	Muscles of mastication and eardrum tension
	General somatic afferent	General sensations from anterior half of head including face, nose, mouth, and meninges
VI. Abducent nerve[a]	General somatic efferent	Movements of eyes
VII. Facial nerve[b]	Special visceral efferent	Muscles of facial expression and tension on ear bones
	General visceral efferent (parasympathetic)	Lacrimation and salivation
	Special visceral afferent	Taste
	General visceral afferent	Visceral sensory
VIII. Vestibulocochlear nerve	Special somatic afferent	Hearing and equilibrium
IX. Glossopharyngeal nerve[b]	Special viscera] efferent	Swallowing movements
	General visceral efferent (parasympathetic)	Salivation
	Special visceral afferent	Taste
	General visceral afferent	Visceral sensory
	Special visceral efferent	Swallowing movements and laryngeal control
X. Vagus nerve[b] and cranial root of XI	General visceral efferent (parasympathetic)	Parasympathetics to thoracic and abdominal viscera
	Special visceral afferent	Taste
	General visceral afferent	Visceral sensory
XI. Spinal accessory nerve (spinal root)	Special visceral efferent	Movements of shoulder and head
XII. Hypoglossal nerve[a]	General somatic efferent	Movements of tongue

[a] *In addition, there are GSA fibers for proprioception from the muscles of the eye (III, IV, VI) and tongue (XII).*
[b] *In addition, there are GSA fibers for cutaneous sense from just behind the external ear (VII, IX, and X).*

innervating branchiomeric muscles are classified as visceral because of their association with the visceral functions of eating and breathing, not because they are part of the autonomic nervous system. The lower motoneurons are morphologically and functionally identical to motoneurons that supply the somatic musculature. The nerves with special visceral efferent fibers are as follows:

Trigeminal (V)
Facial (VII)
Glossopharyngeal (IX)
Vagus (X)
Spinal accessory (XI)

The SVE components of these nerves are distributed amongst the branchial arches as follows: the first arch (jaw) by n.V, the second (hyoid) arch by n.VII, the third arch by n.IX, and the remaining arches by nerves X and XI. Three of the nerves (facial, glossopharyngeal, and vagus) also contain parasympathetic fibers (GVE), SVA fibers subserving taste, and general visceral afferent fibers (GVA) (*see* **Table 14.1**). Although the accessory nerve contains

only lower motoneurons categorized as SVE, and thus technically is not a mixed nerve, it is regarded as part of the vagus system.

GANGLIA IN THE HEAD

The named ganglia in the head are of two types: (1) sensory ganglia containing the cell bodies of neurons of the first order (equivalent to dorsal root ganglia of the spinal cord), and (2) parasympathetic ganglia. The *sensory ganglia*, including their associated cranial nerves and functional components, are the trigeminal (Gasserian, semilunar) ganglion and mesencephalic nucleus of n.V (GSA), geniculate ganglion of n.VII (GVA, SVA, and GSA), vestibular and spiral ganglia of n.VIII (SSA), superior (GSA), and inferior (SVA) ganglia of n.IX; and superior (GSA) and inferior (SVA) ganglia of n.X (*see* **Fig. 14.2**). The mesencephalic nucleus of n.V is unique in that it consists of cell bodies of the trigeminal ganglion that are displaced to the brainstem.

The *parasympathetic* ganglia (GVE), where preganglionic fibers synapse with postganglionic neurons, include the ciliary ganglion of n.III, pterygopalatine (sphenopalatine) and submandibular ganglia of n.VII, and the otic ganglion of n.IX (*see* **Fig. 14.3**). The numerous ganglia of the vagus nerve (n.X) are located in or near organs of the body (e.g., heart and gastrointestinal tract; *see* **Fig. 20.3**).

CRANIAL NERVE NUCLEI WITHIN THE BRAINSTEM

Sensory nuclei where afferent fibers terminate (called terminal nuclei) and the nuclei of origin of motor fibers of the cranial nerves are organized in discontinuous nuclear "columns" within the brainstem. The olfactory nerve (n.I, SVA) and the optic nerve (n.II, SSA) are telencephalic derivatives, not brainstem cranial nerves.

Sensory Nuclei of Termination (*see* Fig. 14.2)

The *special somatic afferent column* includes the *vestibular* and *cochlear nuclei* (n.VIII), which are located in the posterolateral tegmentum of the upper medulla and lower pons. The *general somatic afferent column* includes the *mesencephalic nucleus of n.V* (proprioception), consisting of scattered clusters of first order neurons in the posteromedial midbrain tegmentum, the p*rincipal (chief* or *main) sensory nucleus of n.V* (touch), located in the lateral midpontine tegmentum, and the *spinal trigeminal nucleus* (pain and temperature), located in the lateral tegmentum of the lower pons, medulla, and the upper two cervical spinal cord segments (fibers from nerves V, VII, IX, and X terminate in these nuclei). The *visceral afferent column* consists of the *nucleus solitarius* located in the midposterior tegmentum of the medulla; its components include taste (SVA) and other visceral fibers (GVA) that enter the brainstem via cranial nerves VII, IX and X.

Motor Nuclei of Origin (*see* Fig. 14.3)

The *general somatic efferent column* includes *nuclei of the oculomotor nerve* (midbrain), *trochlear nerve* (lower midbrain), *abducent nerve* (lower pons), and *hypoglossal nerve* (medulla). These nuclei, located in the posteromedial tegmentum, are composed of lower motoneurons innervating the voluntary muscles of the eye and tongue.

The *special visceral (branchial) efferent column* includes the *motor nucleus (masticator nucleus) of the fifth nerve* (midpons, n.V), *motor nucleus of the seventh nerve,* usually referred to as the *facial nucleus* (lower pons, n.VII), and *nucleus ambiguus* (medulla, nerves IX, X, and XI). The nuclei of lower motoneurons to branchiomeric muscles are located in the middle of the tegmentum. The fact that these alpha motoneurons are morphologically identical to those of the general somatic efferent nerves cannot be overemphasized

The *general visceral efferent column* includes the *accessory oculomotor nucleus of Edinger–Westphal* (midbrain, n.III), the *superior salivatory nucleus* (posterior tegmentum of lower pons, n.VII), the *inferior salivatory nucleus* (posterior tegmentum of upper

medulla, n.IX), and the *dorsal motor nucleus of the vagus nerve* (posterior tegmentum of medulla, n.X). These nuclei are composed of cell bodies of preganglionic parasympathetic neurons of the autonomic nervous system. The salivatory nuclei are intermixed with other neurons in the tegmentum and identifiable only by physiologic techniques.

SOME FUNCTIONAL AND CLINICAL CONSIDERATIONS

Olfactory Nerve (n.I)

The olfactory nerve (SVA) is composed of unmyelinated axons that extend from the nasal mucosa to the olfactory bulb. Villi, with recep-

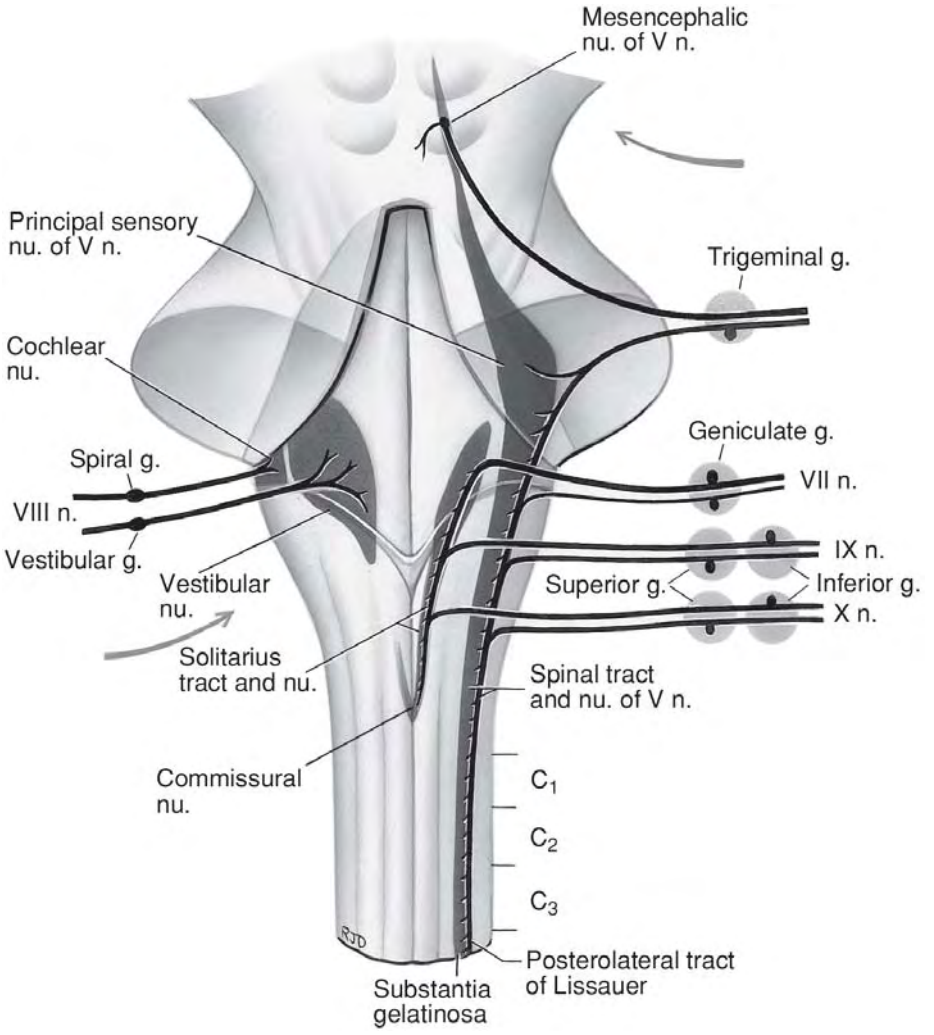


Figure 14.2: Location of the afferent (sensory) cranial nerve nuclei within the brainstem, which form three columns. The superior and inferior ganglia of the ninth and tenth cranial nerves are unlabeled.

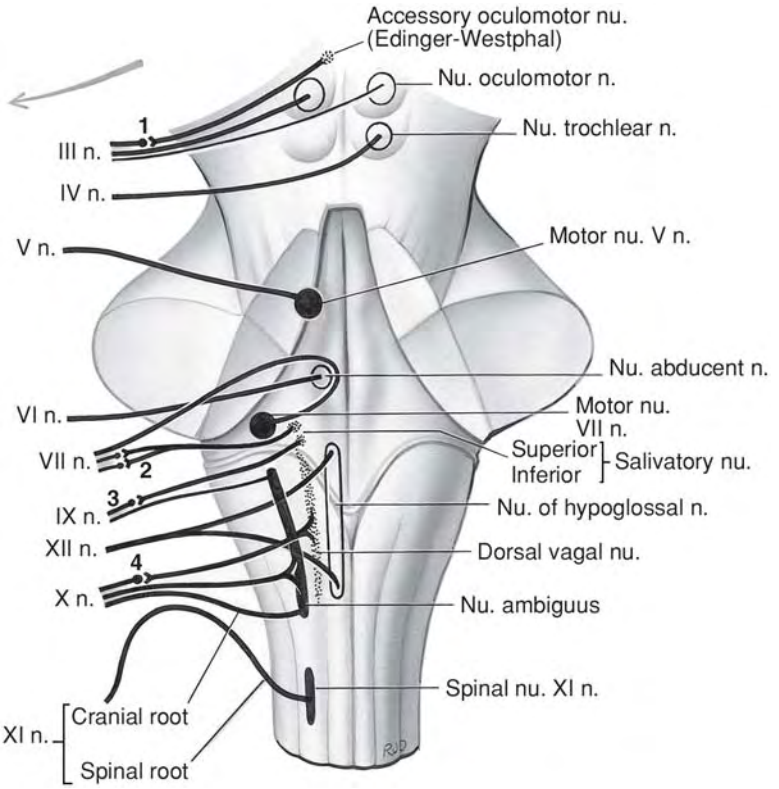


Figure 14.3: Scheme of the efferent (motor) cranial nerve nuclei within the brainstem, which form three columns. Arabic numerals indicate parasympathetic ganglia: (1) ciliary ganglion, (2) pterygopalatine and submandibular ganglia, (3) otic ganglion and (4) terminal ganglia.

tors, protrude from the dendrites of the olfactory *receptor neurons* (ORNs) into the olfactory portion of the nasal mucosa. The axons of the olfactory nerve are grouped into bundles wrapped by a single neurolemma cell (*see* Fig. 2.8B). The ORNs are unique in that each serves as a chemoreceptor, transducer, and as a first-order neuron. As a receptor, it responds directly to environmental chemicals that are sensed as odors; as a transducer, it evokes graded potentials; as a first-order neuron, it conducts nerve impulses to neuronal complexes within the olfactory bulb (*see* **Figs. 1.9 and 22.2**).

Optic Nerve (n.II)

Bipolar cells of the retina are the SSA first-order neurons of the visual pathway. The optic nerve is actually a tract of the brain composed of axons of retinal ganglion cells, and as a tract it does not regenerate when interrupted (Chap. 19).

Oculomotor (n.III), Trochlear (n.IV) and Abducent (n.VI), Nerves (*see* Fig. 14.4)

These cranial nerves have lower motoneurons (GSE) that innervate the extraocular voluntary muscles and the levator palpebrae muscle (eyelid). The integrated actions of these nerves are responsible for *conjugate movements of the eye* (called gaze; simultaneous movement of the two eyes in the same direction). Each nerve contains proprioceptive (GSA) fibers, which can have cell bodies along the nerve, in the trigeminal ganglion or in the mesencephalic nucleus of n.V. The third nerve contains preganglionic parasympathetic (GVE)

fibers that synapse with postganglionic neurons in the ciliary ganglion. They are part of the pathway for accommodation and pupillary constriction (Chap. 19).

Functional Role of the Extraocular Muscles. Control of eye movements is complex, the action of an individual muscle varying with the position of the eyeball within the orbit. The following account is schematic. Nerve III innervates the levator palpebrae, superior rectus, inferior rectus, medial rectus, and inferior oblique muscles. Nerve IV innervates the superior oblique muscle, and nerve VI innervates the lateral rectus muscle. The integrated activity of these muscles results in horizontal, vertical, oblique, and convergence movements (Chap. 19). The levator palpebrae elevates the

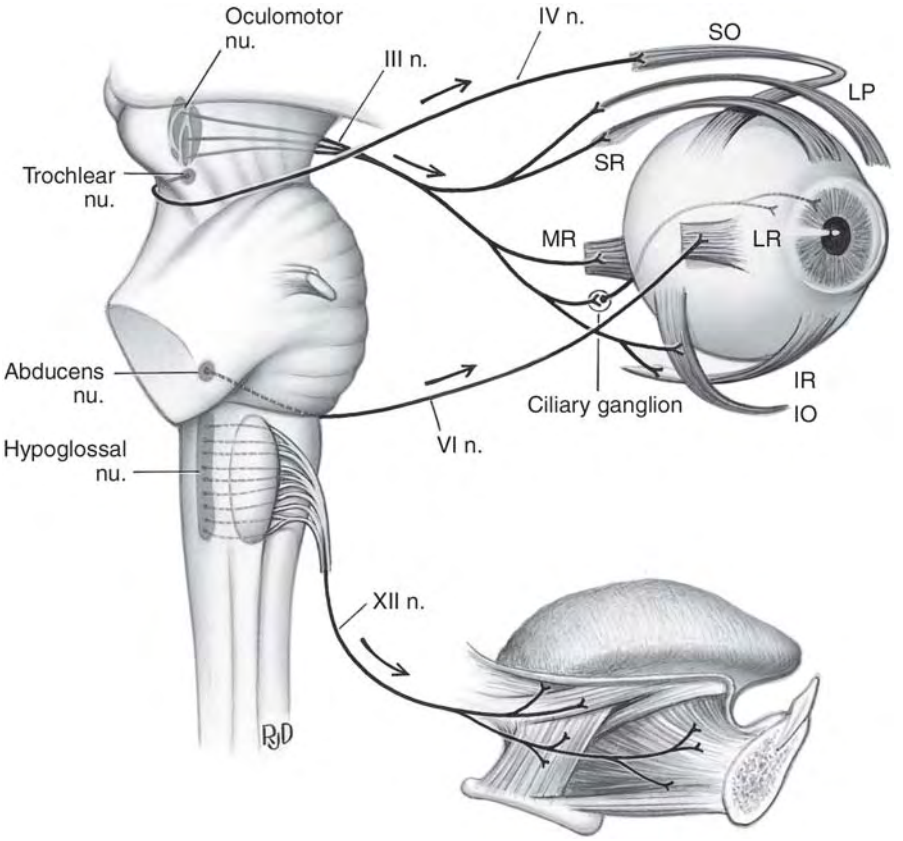


Figure 14.4: Scheme of the nuclei (nu) and distribution of the general somatic efferent cranial nerves: oculomotor, III; trochlear, IV; abducent, VI; and hypoglossal, XII. The extraocular muscles innervated by the oculomotor nerve are the inferior oblique (IO), inferior rectus (IR), medial rectus (MR), and superior rectus (SR). In addition, the oculomotor nerve supplies the levator palpebrae superioris (LP), which elevates the upper eyelid. Parasympathetic preganglionic fibers from the Edinger–Westphal subdivision of the oculomotor nucleus go to the ciliary ganglion; postganglionics innervate the sphincter of the iris (constriction of pupil) and the ciliary muscles (accommodation). The trochlear nerve innervates the superior oblique (SO) and the abducent nerve innervates the lateral rectus (LR). The hypoglossal nerve innervates the intrinsic muscles (longitudinal, vertical and transverse) of the tongue, and the styloglossus innervates hypoglossus and genioglossus muscles.

eyelid. The medial rectus is an *adductor* of the eye (pupil directed to nose), and the lateral rectus is an *abductor* (pupil directed to temple); these muscles move the eyeball in the horizontal plane. In lateral gaze, the medial rectus of one eye and the lateral rectus of the other eye contract synergistically. During convergence, both medial recti contract simultaneously (Chap. 19). In contrast, the action of the muscles responsible for vertical eye movements—superior and inferior recti and superior and inferior oblique muscles—are influenced by the position of the eyeball in the orbit. The superior rectus elevates the eye (pupil up); the elevation increases with abduction. The inferior rectus depresses (pupil down); the depression increases with abduction.

The superior oblique intorts (rotation of upper portion of eye medially toward the midline) the abducted eye and depresses (moves pupil down) the adducted eye. Intorsion increases with greater abduction, and depression increases with greater adduction. The inferior oblique extorts (lateral rotation of the upper portion of the eye away from the midline) the abducted eye and elevates the adducted eye.

Lesion of the Oculomotor Nerve. Ocular convergence occurs when viewing a close object; it keeps the image precisely aligned on the fovea of both eyes (Chap. 19). Except for convergence, all normal eye movements are conjugate, i.e., the two eyes turn so that their visual axes remain parallel. The paralysis of one or more extraocular muscles results in *diplopia* (double vision) as a result of faulty conjugate movements. A complete lesion of an oculomotor nerve produces the following: (1) drooping of the eyelid (*ptosis*) and inability to elevate it because of unopposed action of the orbicularis muscle, which closes the eyelid (innervated by n.VII); (2) dilated pupil (*mydriasis*) and unresponsiveness of eye reflexes to light (pupillary constrictor and ciliary muscle paralysis from third nerve injury and the unopposed action of pupillary dilator muscle, which is innervated by the intact sympathetic fibers); (3) pupils of unequal size (anisocoria); (4) external *strabismus,* with the eye abducted and unable to move inward, upward, and downward. This horizontal diplopia is the result of the unopposed action of the lateral rectus and the superior oblique muscle. The eye cannot be adducted or elevated.

Lesion of the Trochlear Nerve. A complete lesion of the trochlear nerve results in a vertical diplopia, head tilt, and limitation of ocular movement on looking down and in. Diplopia is maximal when the eyes are directed downward; this makes it difficult for the subject to descend stairs. To align the eyes in order to minimize or eliminate the diplopia, the patient tilts his head to the shoulder of the side opposite the paralyzed muscle. Because the trochlear nerve decussates within the brainstem, the trochlear nucleus is located on the side opposite to that of its nerve; hence, a lesion of a nucleus of the trochlear nerve is expressed in the contralateral eye.

Lesion of the Abducent Nerve. A complete lesion of the abducent nerve results in a horizontal diplopia, with the ipsilateral eye adducted, because of the unopposed action of the normal medial rectus muscle. The diplopia is maximal when the subject attempts to gaze to the side of the lesion (because the eye with the paralyzed lateral rectus muscle cannot be adequately abducted). It is minimal with gaze to the normal side because the visual axis of the normal eye can be aligned with that of the affected eye.

Trigeminal Nerve (n.V) (*see* Fig. 14.5)

The trigeminal nerve branches into three divisions: ophthalmic, maxillary, and mandibular (*see* **Fig. 14.5**). Each division supplies a distinct region; there is no overlap in contrast with the dermatomal overlap of spinal roots (*see* **Figs. 9.5 and 10.6**).

The sensory fibers enter at the midpons level as the *sensory root (portio major)*, whereas the *motor fibers* emerge through the adjacent *motor root (portio minor)*.

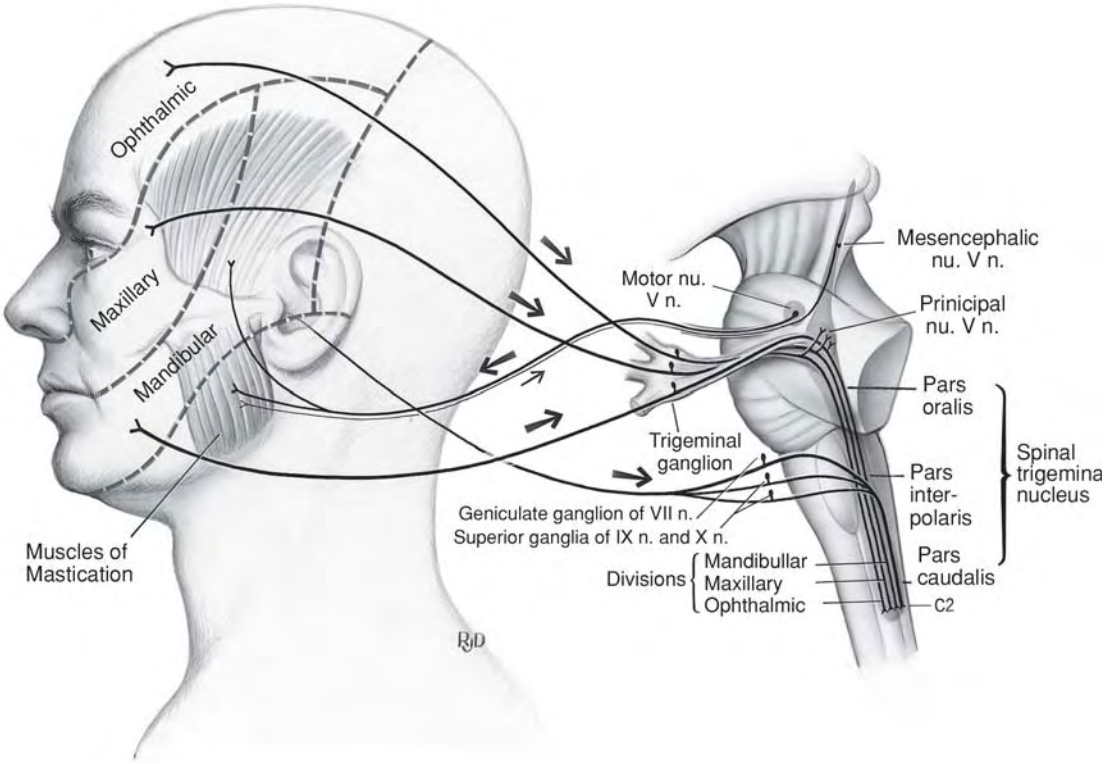


Figure 14.5: The cranial nerve nuclei and distribution of the trigeminal nerve (n.V). The nerve has three divisions: ophthalmic (I), maxillary (II), and mandibular (III). The three sensory nuclei (mesencephalic, principal, and spinal) of the nerve form a continuous column from the level of the superior colliculus to spinal cord level C2. The sensory nuclei are somatotopically organized. Because of rotation of the nerve root, mandibular fibers are most dorsal and ophthalmic fibers most ventral. The spinal trigeminal nucleus, divided into pars, oralis, interpolaris, and caudalis, also receives input from primary fibers that innervate the region of the external ear via the seventh nerve (geniculate ganglion) and nerves IX and X (superior ganglia).

Sensory Root. The sensory input (GSA) is conveyed via first-order fibers (with cell bodies in the trigeminal ganglion) from the skin of the scalp anterior to the coronal plane through the ears. The innervated region comprises the face, orbit, mucous membranes of the nasal cavity, nasal sinuses and oral cavities, teeth, and most of the dura mater. These first-order neurons terminate in the principal sensory nucleus and the spinal trigeminal nucleus of n.V (*see* **Figs. 9.5, 10.6, and 14.5**).

Cell bodies of first-order neurons mediating proprioception form the mesencephalic nucleus of n.V. This nucleus receives input via the mandibular nerve from the muscles of mastication and from pressure receptors in the periodontal ligaments of the teeth. There is a monosynaptic relay to the lower motoneurons of the motor nucleus of n.V to complete a two-neuron arc that mediates the jaw reflex (similar to the knee jerk reflex). The mesencephalic nucleus also receives proprioceptive input from the extraocular muscles.

Motor Root. The lower motoneuron fibers from the motor nucleus of n.V (SVE) pass through the motor root and the mandibular division before innervating the jaw muscles of

mastication (masseter, pterygoids, and temporalis muscles), tensor tympani and some other muscles. The *jaw jerk reflex* is evoked by tapping the chin of the slightly opened mouth with a reflex hammer (*see* **Fig. 10.6**).

Lesion of the Trigeminal Nerve. Interruption of all trigeminal nerve fibers unilaterally results in (1) anesthesia and loss of general senses in the regions innervated by n.V and (2) a lower motoneuron paralysis (loss of jaw reflex and fibrillations, weakness and atrophy of jaw muscles). The sensory changes include loss in the ipsilateral nostril of the sensitivity of the nasal mucosa to ammonia and other volatile chemicals (smarting effect) and a loss of corneal sensation on the same side. The interruption of sensory fibers from the cornea (ophthalmic division) produces a loss of the ipsilateral and contralateral (consensual) corneal reflex (Chap. 19). Fibers forming the afferent limb of the corneal reflex terminate in the spinal trigeminal nucleus, pars oralis (*see* **Fig. 9.5**), which projects bilaterally to the facial nucleus (n.VII). The latter innervate the orbicularis oculi muscles that close the eyes (both eyes blink). The loss of proprioceptive input can result in the relaxation of the ipsilateral muscles of facial expression (innervated by n.VII). The loss of the jaw jerk results from the interruption of both the afferent and efferent limbs of the arc. Because of the action of the contracting pterygoid muscles on the normal side, the jaw, when protruded, will deviate and point to the paralyzed side.

Sharp, agonizing pain localized over the distribution of one or more branches of the trigeminal nerve is known as *trigeminal neuralgia* or *tic douloureux*. This condition (of unknown cause) can be accompanied by muscle twitching (tic) and disturbances in salivary secretion. The stimulation of a region, called a *trigger zone*, can initiate an attack.

The supranuclear influences upon the motor nucleus of n.V are outlined in Chapter 11. Because the motor nucleus of n.V is influenced by both crossed and uncrossed corticobulbar and corticoreticular pathways, unilateral supranuclear (upper motoneuron) lesions usually do not impair trigeminal motor activity.

Facial Nerve (n.VII) (*see* Fig. 14.6)

The facial nerve consists of (1) the *facial nerve proper* or *motor division* comprised of lower motoneurons (SVE) and (2) the *nervus intermedius* with sensory (GSA and SVA) and parasympathetic components (GVE). All cell bodies of first-order sensory neurons are in the *geniculate ganglion*. The GVA input from the viscera in the soft palate and tonsillar region and the SVA (taste) input from the anterior two-thirds of the tongue terminate in the nucleus solitarius (*see* "Gustatory Nucleus"). Fibers from the motor nucleus of n.VII (SVE) take a hairpin course through the lower pons (they recurve as the internal genu around the nucleus of n.VI) before emerging into and passing through the cerebellopontine angle. These fibers innervate the muscles of facial expression, including the orbicularis oculi (closes eyelid and protects eye), buccinator (moves cheek), and stapedius (moves stapes bone) muscles. Parasympathetic preganglionic fibers from the superior salivatory nucleus make synaptic connections with postganglionic neurons in the pterygopalatine and submandibular ganglia; these fibers stimulate the lacrimal, nasal, oral, submaxillary and sublingual glands, and blood vessels.

Lesion of the Facial Nerve. A lesion interrupting the facial nerve (e.g., *Bell's palsy*) is primarily expressed as a lower motoneuron paralysis of the muscles of facial expression. The paralysis of Bell's palsy can occur suddenly, followed within a few months by a spontaneous recovery. On the ipsilateral side, the forehead is immobile, the corner of the mouth sags, the nasolabial folds of the face are flattened, facial lines are lost, and saliva can drip from the corner of the mouth. The patient is unable to whistle or puff the cheek because the buccinator muscle is paralyzed. When smiling, the normal muscles draw the contralateral corner of the mouth up while the paralyzed corner continues to sag. Corneal sensitivity remains

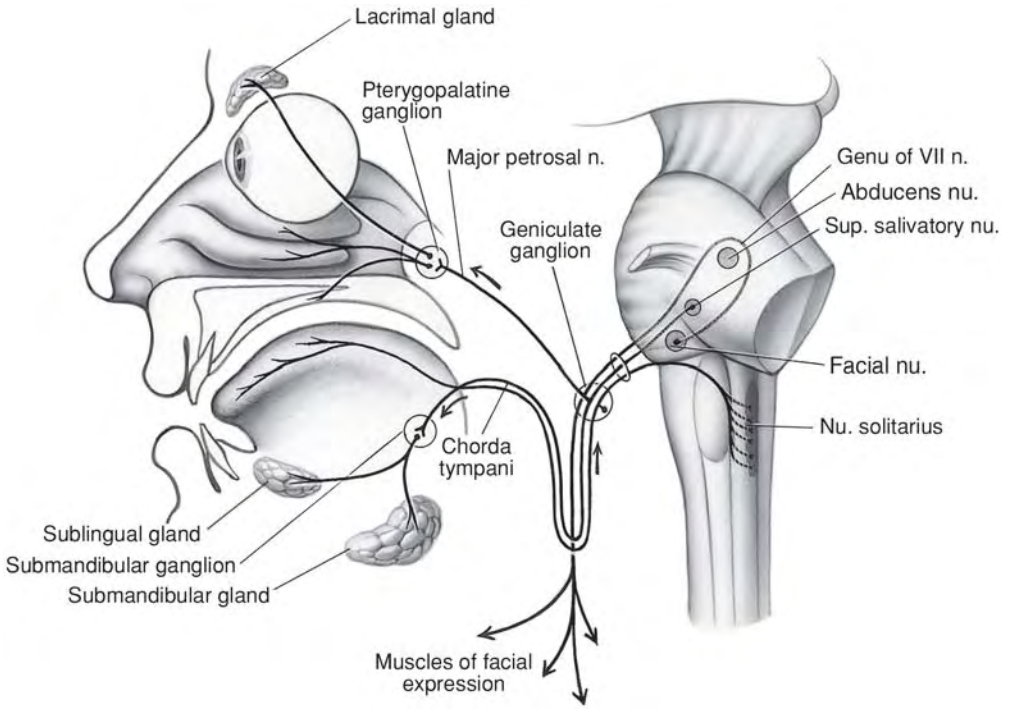


Figure 14.6: The cranial nerve nuclei and distribution of the facial nerve (n. VII).The superior salivatory nucleus is embedded within the reticular formation and cannot be identified in normal brainstem sections.

(n.V), but the patient is unable to blink or close the eyelid (n.VII). To protect the cornea from damage (e.g., drying), therapeutic closure of eyelids or other measures are taken (e.g., patient wears an eye mask or lids are closed by sutures). Lacrimation and salivation on the lesion side can be impaired. Taste will be lost on the ipsilateral anterior two-thirds of the tongue. An increased acuity to sounds (*hyperacusis*) results from paralysis of the stapedius muscle, which normally dampens the amplitude of the vibrations of the ear ossicles. Hyperacusis occurs only to loud sounds, which activate the acoustic reflex (Chap. 16).

When the cornea is touched, the eyelid immediately closes (the *corneal reflex).* The trigeminal nerve forms the sensory limb from the cornea of the eye, and the facial nerve is the motor limb causing the orbicularis oculi muscle to close the eyelid. The closure of the eyelid on the same side as that stimulated is known as the *direct corneal reflex*, whereas the closure of the contralateral eyelid is known as the *consensual corneal reflex*. Stated otherwise, if the facial nerve on one side is completely destroyed, the sensitive cornea cannot evoke a direct corneal reflex but can evoke a consensual corneal reflex. If the fibers of the nervus intermedius on both sides are intact and motor fibers of the facial nerve destroyed on one side, then the direct corneal reflex is absent on that side; however, lacrimal secretion can increase on both sides because of parasympathetic activity.

Supranuclear Facial Palsy. A unilateral supranuclear lesion of the upper motoneurons (corticobulbar and corticoreticular fibers) to the facial nucleus results in a marked weakness of the muscles of expression of the face below the

eye on the side contralateral to the lesion. The frontalis muscle (wrinkles forehead) and the orbicularis oculi muscle (closes eyelid) are unaffected. The accepted explanation states that (1) bilateral upper motoneuron projections from the cerebral cortex terminate on the lower motoneurons, innervating the frontalis muscle and orbicularis oculi, and (2) only unilateral, crossed upper motoneuron projections go to the lower motoneurons, innervating the muscles of facial expression of the lower face. Hence, after unilateral supranuclear lesions, the contralateral muscles are deprived of upper motoneuron influences. In some patients with supranuclear lesions, the weak, lower facial muscles will remain paralyzed to volitional control, but will respond to emotional or mimetic stimuli (joke, distress). The influences that evoke this involuntary response are not known. For more details, refer to Chapters 11 and 17.

Note the distinction between a lower motoneuron lesion and an upper motoneuron lesion involving the muscles of facial expression. In a lower motoneuron paralysis, all of the muscles of facial expression on the same side as the lesion are paralyzed. In an upper motoneuron paralysis following a lesion of the corticobulbar fibers, for example, in the internal capsule, the muscles of facial expression in the lower face below the angle of the eye on the side opposite the lesion are paralyzed.

Vestibulocochlear Nerve (n.VIII)

The cochlear nerve, an exteroceptive nerve concerned with hearing, consists of fibers of bipolar neurons with cell bodies in the spiral ganglion (Chap. 16). Its peripheral fibers innervate the hair cells in the spiral organ of Corti and the central fibers terminate in the dorsal and ventral cochlear nuclei. The vestibular nerve, a proprioceptive nerve concerned with equilibrium and orientation of the head in space, consists of fibers of bipolar neurons with cell bodies in the vestibular ganglion (Chap. 16). Its peripheral processes innervate the cristae (in ampullae of the semicircular ducts) and in the maculae (of utricle and saccule); the central processes terminate in the four vestibular nuclei in the brainstem, and uniquely in the cerebellum (Chap. 18).

Glossopharyngeal Nerve (n.IX) (*see* Fig. 14.7)

The GVA input of n.IX from the palatine, tonsillar, and pharyngeal regions and from the *carotid sinus* (pressoreceptor, arterial pressure) and *carotid body* (chemoreceptor, CO_2 and O_2 concentration in blood) is conveyed via first-order fibers (cell bodies in inferior ganglion) to the nucleus solitarius. The SVA input (taste) from the posterior third of the tongue is relayed via first-order neurons (cell bodies in inferior ganglion) to the gustatory portion of the nucleus solitarius, which is located at its rostral end. Some GSA afferents from the tympanic cavity and external auditory meatus with cell bodies in the superior ganglion terminate in the spinal trigeminal nucleus. The SVE lower motoneurons from the nucleus ambiguus innervate pharyngeal and palatine muscles (effect swallowing) and the stylopharyngeal muscle (elevates upper pharynx). The preganglionic parasympathetic (GVE) component from the inferior salivatory nucleus is relayed via the otic ganglion to the parotid gland.

Disturbances associated with lesions of n.IX, include (1) unilateral loss of taste in the posterior third of the tongue, (2) unilateral loss of the *gag (pharyngeal) reflex*, and (3) unilateral loss of the carotid sinus reflex. Glossopharyngeal neuralgia (similar to trigeminal neuralgia) can be triggered by chewing or swallowing.

Vagus Nerve (n.X) (*see* Fig. 14.8)

The vagus nerve has not only general and special visceral afferent components, but general and special visceral efferent components as well (*see* **Table 14.1**). In addition, there is a general somatic afferent component. The GVA input is from the respiratory system (larynx, trachea, and lungs), cardiovascular system (carotid sinus and body, heart, and various blood vessels), gastrointestinal tract, and dura mater in the posterior fossa. The peripheral processes extend from the organs to the cell bodies located in the inferior ganglion located

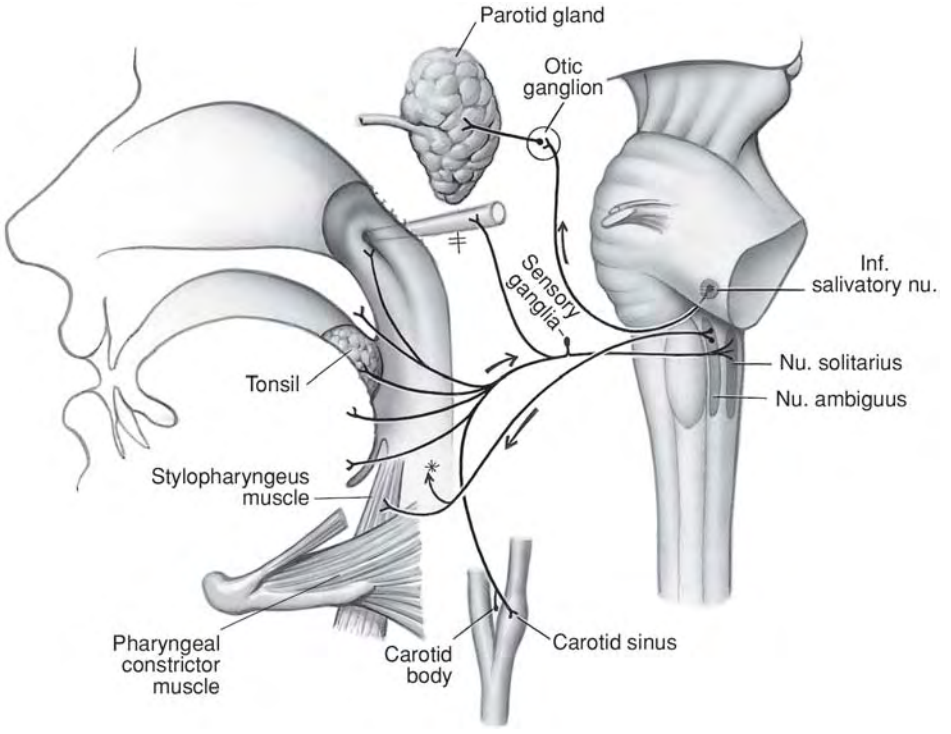


Figure 14.7: The cranial nerve nuclei and distribution of the glossopharyngeal nerve (n. IX). This nerve supplies motor innervation to the stylopharyngeus muscle, the muscles (*) of the anterior and posterior pillars of the fauces, and, possibly, some superior pharyngeal muscle fibers involved in deglutition. The inferior salivatory nucleus is embedded within the reticular formation. ‡, auditory tube.

adjacent to the medulla; the central processes terminate in the nucleus solitarius. The SVA fibers mediate taste. Their peripheral processes originate in the epiglottis and extend to cell bodies in the inferior ganglion adjacent to the medulla; central processes terminate in the gustatory portion of the nucleus solitarius.

The GVE component consists of preganglionic parasympathetic fibers from the dorsal vagal nucleus that project to terminal ganglia close to their target structures. From there, postganglionic neurons go to the cardiovascular, respiratory, and gastrointestinal systems of the thorax and abdomen. A GVE influence to the heart itself is conveyed over preganglionic parasympathetic neurons from cells that might be located close to the nucleus ambiguus. The SVE output takes origin from lower motoneurons in the nucleus ambiguus that innervate the voluntary muscles of the soft palate, pharynx, and intrinsic laryngeal muscles (some of the fibers from the nucleus ambiguus course via n.XI before joining the vagus nerve).

The GSA component consists of fibers from the tympanic cavity (middle ear) and the external auditory meatus (with cell bodies in the superior ganglion) that terminate in the spinal trigeminal nucleus.

Lesion of the Vagus Nerve. A complete unilateral lesion of the vagus nerve results in the following symptoms: (1) the soft palate is flaccid, producing a voice with a twang (dysphonia); (2) swallowing is difficult (*dysphagia*)

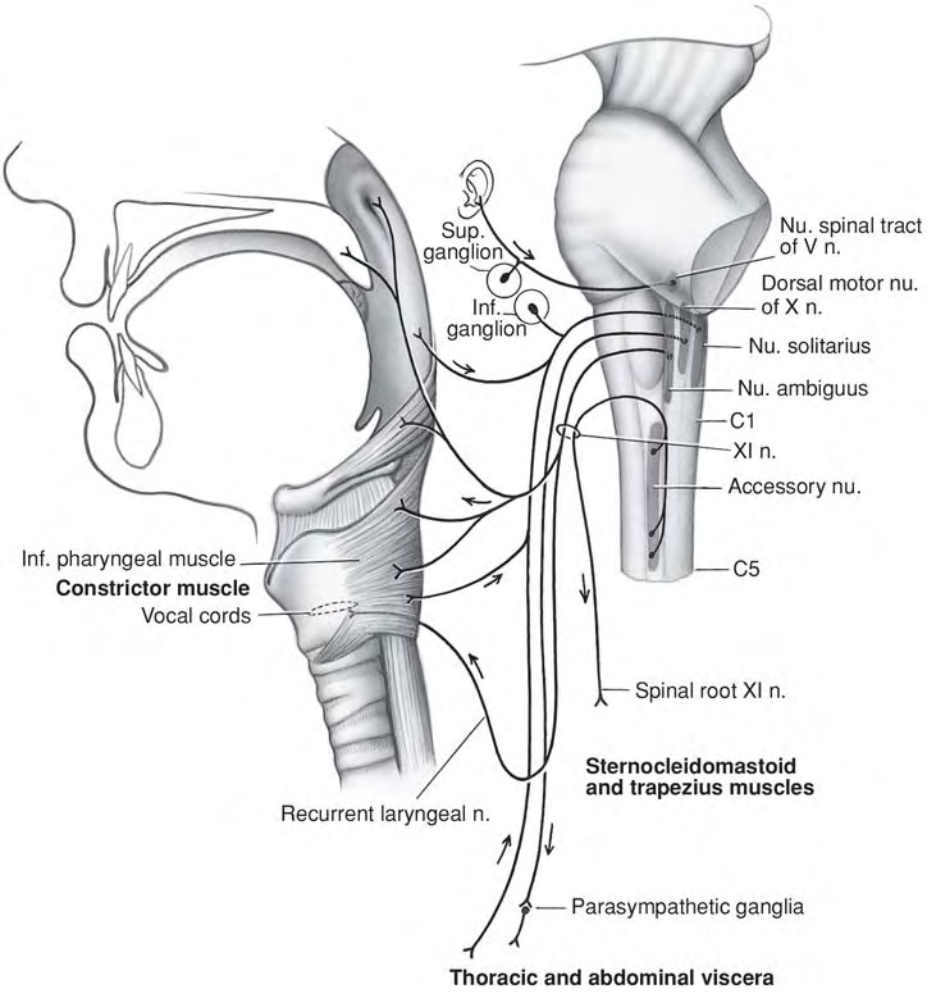


Figure 14.8: The cranial nerve nuclei and distribution of the vagus (n.X) and accessory (n.XI) nerves.

because of a unilateral paralysis of pharyngeal constrictors (the pharynx is shifted slightly to the normal side); (3) difficult or labored breathing (dyspnea). A transient *tachycardia* (increased heartbeat) occurs because of the interruption of some parasympathetic stimulation (*see* subsection Lesion of the Accessory Nerve). Bilateral lesions of the vagus nerve are fatal unless a tracheotomy is done immediately; the larynx is paralyzed and the vocal cords become adducted.

Accessory (Spinal Accessory Nerve (n.XI) (*see* Fig. 14.8)

The accessory nerve consists of two roots, spinal and bulbar (cranial). The fibers of the spinal root originate from anterior horn cells in cervical levels 1 through 5, emerge and ascend alongside the spinal cord (dorsal to the denticulate ligament) and medulla, and join the cranial root in the jugular foramen; the spinal root innervates the ipsilateral sternomastoid and the upper half of the trapezius muscles. The fibers

of the cranial root originate from the nucleus ambiguous course, with n.XI a short distance before branching and joining n.X, and, eventually, form the recurrent laryngeal nerve, which innervates the intrinsic laryngeal muscles.

Lesion of the Accessory Nerve. A lower motoneuron paralysis of the spinal root fibers is revealed by a weakness in the ability to rotate the head so that the chin points to the side opposite the lesion (paralyzed sternomastoid muscle). There is a downward and outward rotation of the upper scapula together with impaired ability to shrug the shoulder and elevate the arm over the head (paralyzed upper trapezius muscle). After a unilateral lesion of the cranial root, the ipsilateral vocal cord becomes fixed and partially adducted; the voice is hoarse (*dysphonia*) and reduced to a whisper. Unilateral injury to the recurrent laryngeal nerve causes partial abduction because of sparing of the motor fibers to the cricothyroid muscle, which travel in the superior laryngeal nerve.

Reflexes Involving Nerves VII, IX, X, and XI

Taste–Salivary Gland Reflex. Following stimulation of the taste receptors, gustatory impulses are conveyed to the rostral end of the nucleus solitarius (gustatory nucleus) from the anterior two-thirds of the tongue, via the facial nerve, and from the posterior third of the tongue, via the glossopharyngeal nerve. Projections from the gustatory nucleus terminate in the parasympathetic neurons of the superior and inferior salivatory nuclei. From these nuclei, preganglionic fibers course through the facial and glossopharyngeal nerves to the sphenopalatine, submandibular, and otic ganglia. Postganglionic fibers innervate the salivary glands and stimulate secretion (Chap. 20).

Carotid Sinus Reflex. Baroreceptors, which are mechanorecptors in the wall of the carotid sinus (located at the bifurcation of the common carotid artery into the external and internal carotid arteries), respond to an increase in blood pressure by increasing the firing rate of nerve impulses in the visceral afferent fibers of the glossopharyngeal nerve to the nucleus solitarius. This nucleus sends fibers to (1) the dorsal vagal (parasympathetic) nucleus and (2) the "vasomotor center" in the rostral ventrolateral reticular formation of the medulla.

The motor limb of the reflex arc, acting through inhibitory efferent fibers of the vagus nerve, decreases the heart rate and the cardiac output. In contrast, the "vasomotor center" sends inhibitory signals via the reticulospinal tract to sympathetic preganglionic neurons (levels T1–T5) of the intermediolateral cell columns of the spinal cord (Chap. 20). This diminishes sympathetic tone, also resulting in a decreased heart rate and cardiac output and, in addition, decreases blood pressure by lowering peripheral resistance through vasodilation of the peripheral blood vessels.

Attacks of *syncope* (fainting) occur in individuals with hypersensitive carotid sinus reflexes when light external pressure (tight collar) is applied to the sinus.

Carotid Body Reflex. The carotid body (located near the carotid sinus) can initiate a sequence of neural events affecting the respiratory cycle. The activation of the chemoreceptors of the carotid body (responding to CO_2, O_2, and pH levels in the blood) increases the frequency of action potentials conveyed via the glossopharyngeal nerve to the nucleus solitarius. From this nucleus, interneurons project to the "respiratory center complex" within the brainstem reticular formation. This center, transmits signals via reticulospinal fibers to the lower motoneuron of the phrenic and intercostal nerves, resulting in inspiratory movements. The accompanying inflation of the lungs stimulates the stretch receptors in the bronchiolar walls to increase the frequency of impulses conveyed via the vagus nerve to the nucleus solitarius. Inhibitory influences from this nucleus to the "respiratory center complex" finally end the inspiratory phase of respiration.

Gag (Pharyngeal) Reflex. Stimulation of the pharyngeal region activates the contraction and elevation of the pharynx. The afferent limb of

this reflex is in the glossopharyngeal nerve to the nucleus solitarius. Interneuronal connections to the nucleus ambiguus stimulate the efferent limb of lower motoneurons, traveling over fibers of the glossopharyngeal and vagus nerves to the voluntary muscles of the palate and pharynx.

Cough Reflex. Generally, coughing occurs following the irritation of the larynx, trachea, and/or bronchial tree. The afferent limb conveys impulses via the vagus nerve to the nucleus solitarius. Interneuronal connections are made with the "respiratory center complex" and with the nucleus ambiguus. The "center" activates the rest of the arc, resulting in forced expiration. The nucleus ambiguus and its lower motoneuron axons stimulate the pharyngeal and laryngeal musculature to participate in the act of coughing.

Hypoglossal Nerve (n.XII) (*see* Fig. 14.4)

Lower motoneurons originating in the hypoglossal nucleus innervate the ipsilateral tongue musculature, including the intrinsic muscles and the genioglossus, styloglossus, and hyoglossus muscles. Interruption of the fibers of n.XII produces an ipsilateral lower motoneuron paralysis of the tongue. The fibrillations that occur during early stages are followed by atrophy of the muscles, which results in a wrinkled tongue surface on the side of the lesion. When protruded, the tongue deviates to the paralyzed side. The deviation is the result of the unopposed contraction of the contralateral genioglossus, which pulls the root of the tongue forward while the paralyzed ipsilateral muscle acts as a pivot. The proprioceptive fibers (GSA) from the tongue muscles are presumed to have cell bodies scattered along the nerve.

CHEMICAL SENSES (OLFACTION AND GUSTATION)

Frankinsense and myrrh, as the scent of God, is a testament to the biblical significance of our chemical senses. A plethora of receptive sites have evolved to detect the diversity of chemical stimuli in the environment. Chemical sensitivity and chemical senses are universal expressions of living organisms. The most conspicuous sensory response of bacteria and primitive protozoans, called *chemotaxis,* is the use of chemical receptors to locate food and adequately oxygenated water and to avoid noxious substances. Vertebrates have chemoreceptors for monitoring chemical conditions of both the internal and external environments. Interoceptive sensors monitor such physiologically significant molecular variables in the blood as carbon dioxide, oxygen, and pH, as well as nutrients (e.g., glucose). The activated receptors initiate the processing of neural signals, resulting in release of neurotransmitters at nerve terminals that control the appropriate responses. The original chemical communication of bacteria and primitive protozoa has not been replaced, but, rather, augmented, accelerated, and localized. The *external environment* in vertebrates is sensed by exteroceptive sensors and expressed as olfaction (smell), gustation (taste), and chemesthesis (common chemical senses, Chap. 9).

Olfaction is of great adaptive importance, sampling odorant information coming from great distances via air currents. Olfactory receptors, located within respiratory structures, are associated with the olfactory nerve and vomeronasal nerve. Gustation is less sensitive and more restrictive in responses. Taste receptors, located with feeding structures, are associated with oral and pharyngeal regions innervated by the facial, glossopharyngeal, and vagus nerves.

In light of the significant responses to, and roles of, odorants and tastants, substances stimulating respectively the senses of smell and taste, it is somewhat puzzling that there are no vernaculars for *anosmia,* the clinical absence of smell, or for *ageusia,* the clinical lack of, or impairment of, taste.

Olfaction

The olfactory system includes the *olfactory nerves*, olfactory pathways, and a complex of

processing centers within the brain. The olfactory receptor neurons (ORNs) are embedded in the olfactory neuroepithelium, roughly 5 cm^2, in the roof of each nasal cavity.

An olfactory receptor neuron is bipolar. A single dendrite is directed toward the mucosal surface, where it forms a knoblike expansion from which several mobile cilia extend into the olfactory epithelium coated with serous fluid that serves as a solvent for the odoriferous stimuli (*see* **Fig. 14.9**). The nonolfactory part of the nasal mucosa is coated with mucus. The unmyelinated axon of the ORN terminates in a spherical synaptic unit called a glomerulus within the olfactory bulb (*see* **Fig. 2.2**). Every ORN functions as a chemoreceptor, transducer, and a transmitter of impulses to a glomerulus (*see* **Fig. 14.9**). Olfactory receptor neurons have a life-span of only 4–8 weeks. The unmyelinated axons are grouped into discrete bundles, wrapped by a single neurolemma cell, that collectively constitute the olfactory nerve. These neurons are continuously replaced throughout life by basal cells, which, like those of the taste buds, are stem cells that differentiate into new functional neurons. The receptor gene family acts (1) to either upregulate or downregulate the rate of replacement of ORNs in response to functional needs and (2) to guide newly generated ORN axons to a designated site in the same glomerulus as its predecessor.

The thousands of different volatile odorants (odorous molecules) in the air are dissolved in the compatible organic molecular and ionic environment of the serous secretion of Bowman's glands that bathe the cilia of the ORNs. The interactions between the odorant molecules and the receptor sites of the ORN cilia activate G-protein-coupled second-messenger systems that lead to graded potentials and action potentials in the axons. Odorant receptor genes of the olfactory receptor neurons form the *largest gene family* of the vertebrate genome (Buck and Axel, 1991). This large multigene family (1000 or so different odorant receptor types) permits discrimination of a wide variety of odorants. Each ORN expresses only one unique type of odorant receptor. Its unmyelinated axon synapses in the olfactory bulb within a single *glomerulus* (*see* **Fig. 14.9**). There is assumed to be a gene for every receptor type. Olfactory receptor neurons with the same odorant receptor occupy small zones of the olfactory mucosa scattered among other ORNs expressing different receptor types. All ORNs of the same receptor type in a zone project to the same glomerulus, where they synapse on dendrites of mitral and tufted cells. This maximizes the functional–collecting role of the olfactory epithelium

Sensory information is extensively processed and refined in the olfactory bulb before it is sent to the olfactory cortex. Glomeruli are the receptive sites for the first stage in the analysis and modulation of olfactory information (*see* **Fig. 14.9**). The axons of the approximately 2 million ORNs converge within 2000 glomeruli; it is estimated that the axons of 25,000 ORNs terminate on individual glomeruli. Following neural processing within the olfactory bulb, an estimated 20–50 relay neurons (mitral and tufted cells) project to higher centers, including the olfactory cortex, reflecting an approximately 100–fold convergence. The primary dendrites of each mitral neuron are also confined to a single glomerulus. Each mitral neuron responds to multiple sets of odorants; mitral neurons of other glomeruli respond to different sets of odorants.

The first of three levels of neural processing referred to as *refinement sites* occur within the olfactory bulb. Each spherical glomerulus contains *synaptic triads* comprised of synapses among ORNs, periglomerular interneurons, and mitral neurons interacting as signal refinement sites: (1) The axons of the ORNs branch profusely and have axodendritic synapses with dendrites of the periglobular interneurons and with the primary dendrites of the mitral cells within the glomeruli and (2) the dendrites of the periglomerular interneurons have inhibitory dendrodendritic synapses with the dendrites of the mitral neurons. These synaptic activities play a role in sharpening and refining sensory information. (3) The periglomerular interneurons, which encircle a glomerulus interconnect

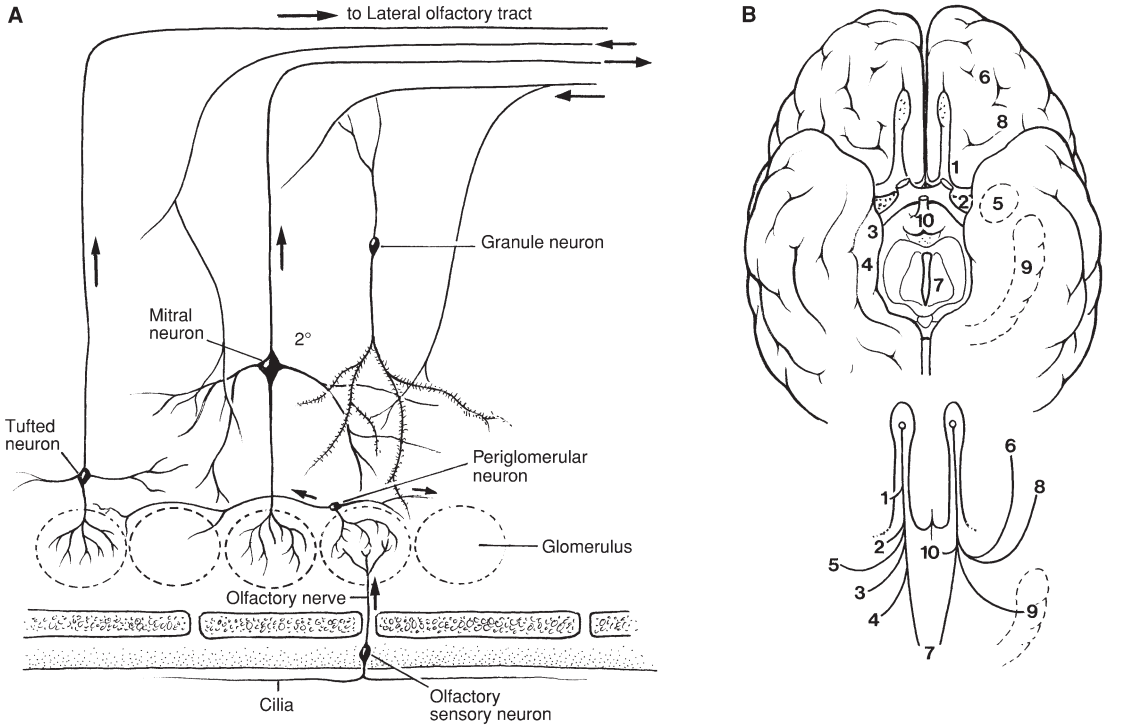


Figure 14.9: Pathways of the olfactory system. The olfactory system is organized for the perception and conscious discrimination of chemical odorants and for activating the limbic system, which is involved in acts of self-preservation and emotive aspects of behavior. (1) When stimulated, receptors of the villi of each odorant receptor neuron (ORN) of the olfactory mucosa generate neural signals that are transmitted via its axon to one glomerulus of the olfactory bulb (*see* Fig. 2.2A). **(A)** A glomerulus, the *initial signal refinement site* where neural processing occurs within each neuronal triad, consists of (a) *axodendritic synapses* of axon terminals of ORNs on the dendritic arbors of periglobular interneurons (PNs) and mitral neurons (MNs) and (b) *reciprocal dendrodendritic synapses* between the dendritic arbors of the PNs and MNs. This is succeeded by a second *signal refinement site* located outside the glomerulus that involves reciprocal dendrodendritic synapses between the dendritic arbors of MNs and granule interneurons (GNs). Input to both of these *signal refinement sites* within the olfactory bulb is derived from centripetal axons arising in centers of the brain and the anterior olfactory nucleus. A similar sequence of synaptic processing applies to the tufted neurons. (2) The output of the olfactory bulb is projected via the olfactory tract by the axons of MNs and their branches to five neuronal centers. These centers include the anterior olfactory nucleus that projects to the contralateral olfactory bulb, the olfactory tubercle of the anterior perforated substance, piriform cortex, entorhinal cortex, and the amygdala. (The axons of tufted neurons terminate in the anterior olfactory nucleus and the olfactory tubercle.) Each of these five higher centers projects directly to the frontal lobe and indirectly to it via a relay in the dorsomedial nucleus of the thalamus, which projects to orbitofrontal cortex. The indirect input is akin to other sensory pathways that reach the cortex via the thalamus. Both frontal cortex and orbitofrontal cortex have roles in the conscious discrimination of odors. Some physiologic, emotional and behavioral responses, expressed in the functional roles of the limbic system, are derived from odorants that activate the olfactory system's projections from the amygdala to the hippocampus and from entorhinal cortex to the hypothalamus (Chaps. 21 and 22). **(B)** Numbers 1 though 10 locate structures in the brain involved with olfaction: (1) anterior olfactory nucleus, (2) olfactory tubercle (3), piriform cortex, (4) entorhinal cortex, (5) amygdala, (6) frontal cortex, (7) thalamus, (8) orbitofrontal cortex, (9) hippocampus, (10) hypothalamus.

by axodendritic synapses and thereby form a screen maintaining the functional integrity of each glomerulus. However, some synaptic communication occurs through a screen to an adjacent glomerulus. The axodendritic synapses between the input ORN and the principal mitral relay cell is the essential linkage for input–output transmission, whereas the inhibitory dendro-dendritic microcircuit synapses between the mitral and tufted relay neurons and the intrinsic periglobular interneurons are involved in control and elaboration of the input–output transfer.

The second level of signal refinement occurs deep in the bulb by negative feedback circuits located outside of the glomerulus, between the granule interneurons and the secondary dendrites (basal dendrites). These dendrodendritic synapses from the mitral neuron to granule interneuron are excitatory, and those from the granule interneuron to mitral neuron are inhibitory (*see* **Fig. 14.9**). This also serves to sharpen and refine olfactory information prior to its transmission via the olfactory tract to the olfactory cortex. In addition, other dendrodendritic synapses are present between the secondary dendrites of the mitral cells and dendrites of some periglobular neurons on the periphery of glomeruli, These inhibitory synapses can form another curtain of inhibition encircling each glomerulus and the region of the secondary dendrites of the mitral neurons.

The third level of neural processing involves the modulatory influences of different centrifugal fiber systems arising from the olfactory cortex (e.g., basal forebrain), locus ceruleus and midbrain raphe nuclei to the activity of the periglobular interneurons and the granule interneurons, These connections can modulate bulb function, signal refinement, and behavioral responses. For example, these influences can enhance the perception of an aroma when searching for food as a response to relieve hunger pangs.

The mitral cells, regarded as the principal relay neurons, convey information to higher regions, including the anterior olfactory nucleus, olfactory tubercle of the anterior perforated space, amygdala, piriform cortex, and entorhinal cortex. The tufted neurons project only to the anterior olfactory nucleus and the olfactory tubercle. The anterior olfactory nucleus has connections with the contralateral olfactory bulb. The other four regions have connections with neural centers likely to be involved with either (1) perception and discrimination of odors or (2) emotional and motivational aspects of smell; they give rise to two pathways; one that bypasses the thalamus and projects directly to frontal cortex and a second that goes to the *orbitofrontal cortex* via a relay in the *dorsomedial nucleus of the thalamus.* Note that the direct projection to the cortex reflects the olfactory system's ancient origin and is unique among sensory systems. The dorsomedial thalamic nucleus can have a comparable role in olfaction to the ventral lateral thalamic nucleus in somesthesis (Chaps. 10 and 11).

The discrimination of odors involves neocortex (orbitofrontal and frontal cortices). Human subjects with lesions of the orbitofrontal cortex are unable to discriminate odors (Buck, 2000). The amygdala and entorhinal cortex, which have connections with the hypothalamus and hippocampus, respectively, are components of the limbic system (Chap. 22). They are associated with emotional and motivational aspects of smell and the behavioral and physiological effects of odors.

Olfactory hallucinations or seizures, referred to as *uncinate fits*, occur in association with other features of epilepsy such as involuntary movements and altered or complete loss of consciousness. They are called uncinate fits because of abnormal electrical activity in the uncus (*see* **Figs. 1.7** and **14.1**) generally producing an unpleasant olfactory reminiscence, which begins the epileptic attack. The uncus encompasses most of primary olfactory cortex including the entorhinal and piriform areas as well as the amygdala.

Accessory Olfactory System. Many mammals have an accessory olfactory system known as the vomeronasal system (VNS) com-

prising paired epithelial vomeronasal organs (VNOs) located adjacent to the nasal septum, vomeronasal nerves, accessory olfactory bulbs, and the amygdala that provide inputs to the hypothalamus and frontal cortex. Chemical communication between members of some species occurs via odors called *pheromones,* which exert important roles in endocrine responses associated with sexual and social behaviors and reproductive physiology (i.e., mating, maternal activities, and establishing territorial boundaries). Relatively few pheromones have been chemically identified. The vomeronasal system is described as rudimentary or absent in humans. The lack of convincing evidence for a functional vomeronasal system in Old World monkeys and apes support the claim that the system as a separate entity does not exist in humans.

Gustation (Taste)

The sense of taste acts at the gateway monitoring both volatile and nonvolatile components of food and drink. Taste combines the recognition and response to a diverse repertory of chemical entities comprising salts, sugars, acids, and a wide array of toxic substances. Taste and smell interact to produce chemosensory experiences and perceptions such as flavor, which can be modified and enhanced by trigeminal "common chemical sense" input and temperature. Gustation is initiated by the response of chemoreceptors of the taste cells of organelles called taste buds (*see* **Fig. 14.10**) that are innervated by the facial, glossopharyngeal, and vagus nerves. Ambient chemicals called *tastants* mediate taste perceptions. Even a "water sense" is indicated; distilled water applied to taste buds evokes discharges in "taste nerve fibers". In humans, taste sensations can be elicited following appropriate stimulation of chemoreceptors on the taste cells of thousands of *taste buds* distributed over the tongue, palate, pharynx, laryngeal surface of the epiglottis, and the upper esophagus. The four taste modalities classically recognized in humans are *salty, sweet, sour, and bitter.* A fifth putative modality is called *umami* ('delicious' in Japanese), which is the flavor of MSG (monosodium glutamate) used in cooking. However, many taste sensations cannot be described in terms of four or five modalities or combinations thereof. Among these are the qualities of numerous spices, fruits, and vegetables. In fact, a truly objective classification has not been developed; probably, there are no primary taste modalities. All are chemically induced sensations. In addition, a form known as "intravascular taste" occurs when certain nutrients such as sugars are injected intravenously. The subjective sensation of taste can be readily modified by many factors, including state of health and hormone levels. The nervous system has a remarkable capacity to recognize a deficiency of certain key nutrients. For example, to correct for a NaCl deficiency, an appetite for salt is induced, resulting in a craving for salty foods (e.g., animals at a saltlick).

Taste buds are microscopic sensors, similar in size to the cell body of an alpha motoneuron of the spinal cord, and are visible to the unaided eye. Each of the some 10,000 taste bud consists of from 40 to 60 elongated bipolar taste (neuroepithelial) receptor cells arranged like the segments of an orange and a smaller basal (stem) cell (*see* **Fig. 14.10**). Currently, elongated *dark cells*, *intermediate cells,* and *light* cells are candidates as representing either three different taste cell types or the developmental phases of one receptor type. Each taste cell has chemoreceptors on several apical microvilli that extend through the common taste pore at the surface of a taste bud into the microenvironment of saliva-containing tastants. At the present time, it is not known whether each taste cell responds to only one tastant or to a composite of tastants. Each taste cell is innervated at its base by branches of several afferent gustatory nerve fibers and each primary nerve fiber has branches that innervate several cells within a taste bud.

Saliva, containing proteins, can contribute to taste sensation by binding to a tastant and expediting its delivery to chemoreceptors in the membranes of the microvilli of the taste cells. The saliva then removes the taste stimulant.

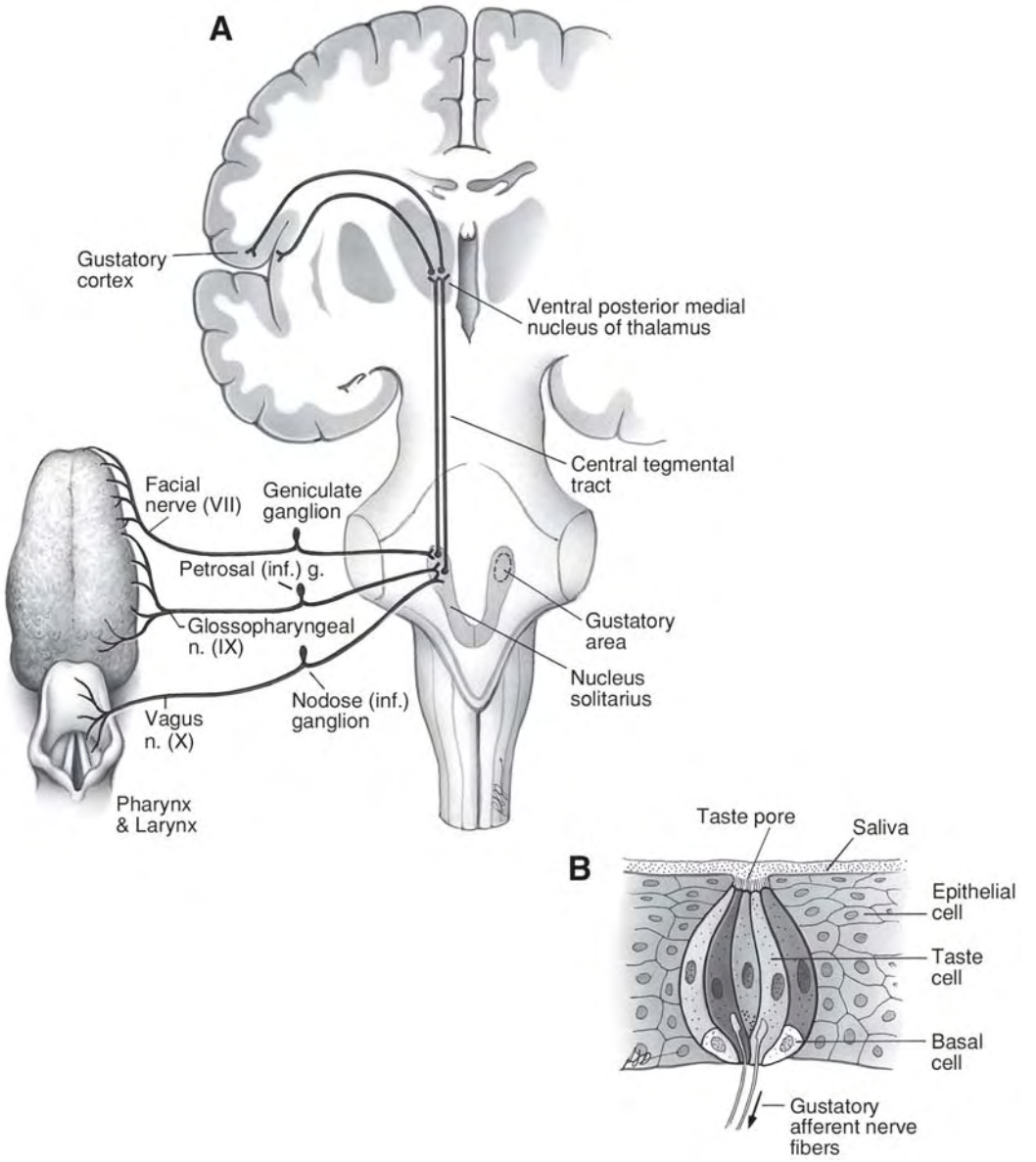


Figure 14.10: Pathway of the gustatory system. **(A)** Chemical molecules stimulate the receptors of the villi of the gustatory receptor cells of taste buds that activate first-order neurons of cranial nerves V, VII, and IX. The axons of these neurons terminate in the "gustatory nucleus," which is within the solitary nucleus. Second-order fibers from the gustatory nucleus ascend ipsilaterally within the reticular formation in the central tegmental tract and terminate in the ventral posterior medial (VPM) nucleus of the thalamus. Third-order fibers from VPM terminate in (1) several centers in the forebrain (e.g., ventral striatum and amygdala) and (2) in primary taste cortex (frontal operculum, rostral insula, and lower postcentral gyrus. **(B)** The flask-shaped taste bud contains a basal cell and three types of receptor cell. Basal cells serve as stem cells that generate a replacement supply of receptor taste cells. The different shading of illustrated receptor taste cells represents either (1) different developmental stages or (2) three separate types of differentiated taste cell.

The mechanisms that serve to transduce sensory stimulation of taste cells to *salty, sour, sweet,* and *bitter* are of two categories: (1) those involved with specific membrane receptors and (2) those based on direct permeation (passing through) or blockage of ion channels.

The detection of *salty taste* stimuli is mediated by Na^+ ion influx through Na^+ channels (direct depolarization by Na^+ ions) and that of *sour taste* stimuli is mediated either by (1) direct depolarization by H^+, (2) direct permeation of Na^+ channels by protons, or (3) proton blockage of K^+ channels. The detection of *sweet stimuli* can result from activation of specific G-protein-coupled receptors on taste cells. *Bitter tastants* are detected in some cases by interactions with ion channels and in other cases by specific G-protein-coupled receptors. *Umami,* the tastant of monosodium glutamate, is considered to trigger the fifth type of taste stimulus. Umami taste is presumed to be associated with a specific type of metabotropic glutamate receptor. The receptors for most taste sensations exhibit a wide range of molecular specificity (e.g., broad tuning), as exemplified by the synthetic sweeteners saccharin and aspartane that are effective in stimulating sweet receptor taste cells.

Taste cells have a short-life span (Apoptotic Death, Chap. 6) and are replaced about every 6–12 days from the *basal cells* of each taste bud. During this cell turnover, the nerve fibers appear to be guided by chemical markers to make synaptic contact with specific types of taste receptor cell. Although the innervation by the taste nerve fibers is essential to maintain the structural and functional integrity of the taste bud, the taste sensibilities of the receptor cells appears to be programmed in the gustatory epithelium itself, not by the afferent nerves. Taste buds degenerate after transection of their sensory innervation; they subsequently reappear following the regeneration of new sensory nerve fibers. This trophic maintenance of each taste bud is apparently dependent on a trophic factor from the nerve. Cranial nerves VII, IX, and X contain the special visceral afferent taste fibers with their cell bodies in the geniculate ganglion (CN VII) and the inferior ganglia of CNs IX and X. With regard to taste, CN VII innervates the anterior two-thirds of the tongue and the palate, CN IX innervates the posterior third of the tongue, and CN X innervates the epiglottis, pharynx, and upper esophagus. The taste buds in different parts of the mouth are differentially sensitive to each of the taste qualities. Sweet taste is best detected at the anterior tip of the tongue, salt in the anterior half of the tongue, sour along the lateral part of the tongue and bitter in the hard palate and the posterior tongue. The gustatory nerves terminate in the rostral *nucleus solitarius,* which is called the *gustatory nucleus* located in the rostral part of the medulla (*see* **Fig. 14.10**). The caudal portion of the nucleus solitarius is the visceral or cardiovascular nucleus. The branches of a single nerve taste fiber can innervate the taste cells in more than one taste bud; this constitutes the receptive field of that nerve fiber. Each taste bud can be innervated by several different afferent fibers and, thus, can contribute to several receptive fields; the taste buds innervated by a single taste neuron can be located on different papillae distributed over a distance of several millimeters. In addition, a taste bud can be innervated by several nerve fibers and thereby be a component of a complex receptive field.

Central Taste Pathway. The central taste pathway differs from those of other sensory systems in that it is exclusively ipsilateral (does not decussate). Axons of the second-order neurons of the gustatory nucleus ascend within the ipsilateral *central tegmental tract* (*see* **Figs. 13.12 to 13.14**) and terminate in the *ventral posteromedial nucleus* (parvicellular part, VPM pc) of the thalamus. Axons from VPMpc pass through the ipsilateral posterior limb of the internal capsule to the *primary taste cortex* (frontal operculum at anterior end of lateral fissure, lower end of postcentral gyrus and rostral insula, mainly area 43). A secondary taste cortex has been described in parts of the orbitofrontal cortex. The various populations of

taste buds express somewhat different sensibilities. They are represented in topographically overlapping patterns throughout the taste pathway. Neurons at all levels of the gustatory pathway are broadly tuned and typically respond to stimuli derived from diverse taste qualities. They respond optimally to one of the four basic taste qualities, but are not specific to just one stimulus. Gustatory neurons readily adapt to constant stimulation. The neurons of the taste pathways become more finely tuned at the higher levels. The multimodal representations of tastes are realized after these finely tuned representations (e.g. 'flavors') are processed in the primary taste cortex, orbitofrontal cortex, and secondary gustatory cortex. The sensation of flavors result from combinations of gustatory, olfactory, and somatosensory inputs. The cerebral cortex mediates the appreciation of these representations of taste. The loss of taste perception (ageusia) can result following a stroke involving the VPM of the thalamus or the primary taste cortex.

Other Neuronal Centers Associated with Taste. The gustatory nucleus also projects to nuclei within the brainstem that are associated with such visceral reflexes as salivation, swallowing, vomiting, digestion, and respiration. Taste areas of the cortex project to other centers of the brain. The perception of the sensations of saltiness, sweetness, sourness, and bitterness generate information that exerts strong influences on the lateral hypothalamus, amygdala, and ventral striatum (nucleus acccumbens). To the tastes of food and drink, the *lateral hypothalamus* has a role in the generation of autonomic responses associated with ingestion and digestion. It can be involved with the reward value food has for hungry animals. The *amygdala,* with its reciprocal connections with the cortical taste areas, presumably is integrated with learning associations between initially derived visual stimuli (e.g., sight of food) and the primary rewards and reinforcement provided by taste. The *ventral striatum* receives influences from the orbitofrontal cortex and the amygdala and some neurons responding to taste stimuli. This neural center can be a part of a system that interfaces reward signals to the motor system where the initiation for action is generated (Chap. 22).

SUGGESTED READINGS

Axel R. The molecular logic of smell. *Sci. Am.* 1995;273:154–159.

Brodal A. *The Cranial Nerves: Anatomy and Anatomico-Clinical Correlations.* 2nd ed. Oxford: Blackwell; 1965.

Brodal A. *Neurological Anatomy in Relation to Clinical Medicine.* 3rd ed. New York: Oxford University Press; 1981.

Buck L, Axel R. A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. *Cell* 1991;65:175–187.

Buck LB. Information coding in the mammalian olfactory system. *Cold Spring Harbor Symp. Quant. Biol.* 1996;61:147–155.

Buck LB. The molecular architecture of odor and pheromone sensing in mammals. *Cell* 2000;100: 611–618.

Doty RL. Olfaction. *Annu. Rev. Psychol.* 2001; 52:423–452.

Doty RL, ed. *Handbook of Olfaction and Gustation.* 2nd ed. New York: Marcel Dekker; 2003.

Finger TE, Silver WL, Restrepo D. *The Neurobiology of Taste and Smell.* 2nd ed. New York: Wiley-Liss; 2000.

Gilbertson TA, Boughter JD Jr. Taste transduction: appetizing times in gustation. *NeuroReport* 2003; 14:905–911.

Gilbertson TA, Damak S, Margolskee RF. The molecular physiology of taste transduction. *Curr. Opin. Neurobiol.* 2000;10:519–527.

Hildebrand JG, Shepherd GM. Mechanisms of olfactory discrimination: converging evidence for common principles across phyla. *Annu. Rev. Neurosci.* 1997;20:595–631.

Kareken DA, Mosnik DM, Doty RL, Dzemidzic M, Hutchins GD. Functional anatomy of human odor sensation, discrimination, and identification in health and aging. *Neuropsychology* 2003;17: 482–495.

Kauer JS, White J. Imaging and coding in the olfactory system. *Annu. Rev. Neurosci.* 2001;24: 963–979.

Korsching S. Olfactory maps and odor images. *Curr. Opin. Neurobiol.* 2002;12:387–392.

Leblanc A. *The Cranial Nerves: Anatomy, Imaging, Vascularisation.* 2nd ed. New York: Springer-Verlag; 1995.

Malnic B, Godfrey PA, Buck LB. The human olfactory receptor gene family. *Proc. Natl. Acad. Sc.i USA* 2004;101:2584–2589.

Matsunami H, Montmayeur JP, Buck LB. A family of candidate taste receptors in human and mouse. *Nature.* 2000;404:601–604.

Mombaerts P, Wang F, Dulac C, et al. The molecular biology of olfactory perception. *Cold Spring Harbor Symp. Quant. Biol.* 1996;61:135–145.

Ranganathan R, Buck LB. Olfactory axon pathfinding: who is the Pied Piper? *Neuron.* 2002;35: 599–600.

Savic I. Imaging of brain activation by odorants in humans. *Curr. Opin. Neurobiol.* 2002;12:455–461.

Seiden A. *Taste and Smell Disorders.* Stuttgart: Georg Thieme Verlag; 1997.

Strausfeld NJ, Hildebrand JG. *Olfactory systems: common design, uncommon origins? Curr Opin Neurobiol.*1999;9:634–639.

Wilson-Pauwels L, Akesson E, Stewart P, Spacey S. *Cranial Nerves in Health and Disease.* 2nd ed. Hamilton Ontario: BC Decker; 2001.

Witkin JW. Nervus terminalis, olfactory nerve, and optic nerve representation of luteinizing hormone-releasing hormone in primates. *Ann. NY Acad. Sci.* 1987;519:174–183.

Zou Z, Horowitz LF, Montmayeur JP, Snapper S, Buck LB. Genetic tracing reveals a stereotyped sensory map in the olfactory cortex. *Nature* 2001;414:173–179.

15
Neurotransmitters as the Chemical Messengers of Certain Circuits and Pathways

Role of Inhibition by Interneurons in Information Processing
Acetylcholine
Amino Acid Transmitters
Biogenic Amines (Monoamines)
Neuropeptides (Neuroactive Peptides)
Nitric Oxide, Carbon Monoxide, and Adenosine

Communication between neurons occurs primarily through the release of neuroactive chemical messengers called *neurotransmitters* or *neuromodulators* (Chap. 3). For a chemical agent to be called a neurotransmitter, it must be synthesized in the presynaptic neuron (acetylcholine and the monoamines are produced in the axon terminals), be stored in presynaptic vesicles and released into a synaptic cleft, bind to a receptor binding site on the postsynaptic membrane of another neuron or effector (muscle fiber or gland cell) where it regulates ion channels, and alter the membrane potential. Finally, it must be removed from the synaptic cleft by reuptake into the presynaptic neuron or by biochemical degradation. Those neuroactive substances that have not been demonstrated to fulfill all of these requirements are often called *putative neurotransmitters*. Some investigators define transmitters as chemical messengers that interact with receptors directly linked to channel proteins, and *neuromodulators* as chemical messengers that interact with a receptor linked to a G-protein and a second-messenger system (Chap. 3). The term neurotransmitter is commonly used to include neuromodulators.

Whether a neuroactive chemical agent elicits an excitatory or an inhibitory response or whether it acts as a neurotransmitter or a neuromodulator is dependent on the receptor protein to which it binds on the postsynaptic membrane. The agent can act as a neurotransmitter when the receptor protein is directly linked to an ion channel protein. Then, the ion selected by the channel determines whether the response is excitatory or inhibitory. Thus, it is possible for a specific transmitter to excite one neuron and inhibit another neuron. Although a variety of agents act as neurotransmitters, the action in the postsynaptic cell depends not on the chemical properties of the transmitter but, rather, on the properties of the receptors that recognize and bind transmitters. For example, acetylcholine (ACh) produces postsynaptic excitation at the neuromuscular junction by acting on a special type of excitatory ACh receptor. In contrast, ACh slows the heart by acting on a special type of inhibitory ACh receptor.

Transmitters at ionotropic receptors produce rapid phasic responses by altering the state of ion channels in the postsynaptic membrane. The agent can act as a neuromodulator or as a neurotransmitter when the receptor protein to which it binds on the postsynaptic membrane is linked to a G-protein. The subsequent interactions of the G-protein and the second-messenger system with the ion channels will then designate the response (Chap. 3). Transmitters at metabotropic (G-protein-coupled) receptors evoke slowly responding longer-lasting effects.

ROLE OF INHIBITION BY INTERNEURONS IN INFORMATION PROCESSING

Lateral inhibition is an important physiological process that is utilized in information processing by all sensory systems. In this process, inhibition (e.g., by inhibitory interneurons) reduces (modulates) the intensity of a strongly excited response (the signal) relatively less than a weakly excited response (the noise) and, thus, enhances the signal-to-noise ratio. For example, lateral inhibition (Chap. 3) enhances odor sensitivity by granule cells in the olfactory bulb (Chap. 14) and luminance contrast by amacrine cells in the retina (Chap.19). Two transmitters involved in these processes are GABA and dopamine.

The chemical messengers that are presumed to be neurotransmitters or neuromodulators comprise more than 50 neuroactive substances. They have been classified as (1) *small-molecule transmitters* and (2) *neuropeptides (neuroactive peptides).* The former are of three types: (1) *Acetylcholine* is the only low-molecular-weight transmitter not derived from an amino acid; (2) the four amino acids are *gamma amino butyric acid (GABA), glycine, glutamate,* and *aspartate;* (3) the four biogenic monoamines include the three catecholamines *norepinephrine (noradrenaline), epinephrine (adrenalin),* and *dopamine*, all derived from the amino acid *tyrosine*, and *serotonin,* derived from the amino acid *tryptophan.* The numerous neuropeptides include such putative neuromodulators as (1) *opioid peptides,* (2) *gastrointestinal (gut–brain) peptides,* and *cardiac/renal and tachykinins*, such as *substance* P, and (3) *hypothalamic releasing peptides* and *neurohypophyseal peptides,* which act as stress regulatory hormones.

Neurotransmitters, neuromodulators, and receptors have been categorized in several ways. In one classification, the neuroactive messengers that usually act (1) as neurotransmitters are acetylcholine and the amino acids listed earlier, and (2) as neuromodulators are the biogenic amines and neuropeptides. Some chemical messengers can belong to both classes depending on the receptor. For example, ACh acts as neurotransmitter interacting with nicotinic ACh receptors that elicit fast excitatory responses through the neuromuscular junction on voluntary muscles. In contrast, ACh acts as a neuromodulator interacting with muscarinic ACh receptors that elicit slow inhibitory responses on cardiac muscle.

Some mature neurons release only one transmitter or modulator at all of its synapses. Others release multiple chemical messengers, small-molecule transmitters, as well as neuroactive peptides. The coexistence of multiple messengers in different vesicles in an axon terminal is still a matter of considerable discussion. In a broad context, this dual presence expands the means by which a neuron can convey complex messages with subtle signal content. The neuropeptide can act to augment what the primary transmitter is programmed to accomplish, as, for example, by strengthening or prolonging the action of the transmitter. The responses of a postsynaptic neuron to a combination of transmitters can vary depending on the amounts and proportions of the messengers released.

Chemical synapses are characterized both by their agents and by the receptor type or various subtypes on which they act. Fourteen serotonergic receptor subtypes have been described on one postsynaptic membrane that interacts with an agent. Some axon terminals can have their own receptors, called *autoreceptors,* that respond to the chemical messenger released at the terminals; they have a role in regulating transmitter release (*see* **Fig. 3.10**). Transmitters and modulators identify chemical systems that delimit complex neural pathways (*see* **Figs. 15.1 to 15.3**).

ACETYLCHOLINE

Acetylcholine is a small-molecule transmitter synthesized from acetylcoenzyme A and choline and catalyzed by the enzyme choline

acetyltransferase. It is degraded in the synaptic cleft by the enzyme acetylcholine esterase (Chap. 3). Neurons that release ACh are known as cholinergic neurons. Both of these enzymes are synthesized in the cell body and conveyed by fast axoplasmic transport to the axon terminal, where the production of ACh takes place (Chap. 3).

About 10,000 molecules of ACh are packaged into each synaptic vesicle. Upon release from the presynaptic terminal into the synaptic cleft, some ACh diffuses rapidly to reach postsynaptic receptors. The remaining ACh is quickly hydrolyzed by the enzyme acetylcholinesterase or removed by diffusion from the synaptic cleft. Some choline is recycled in the terminal. There are two basic types of receptor for ACh. The *nicotinic receptor* is an ionotropic receptor, whereas the *muscarinic receptor* is metabotropic. Certain drugs that simulate ACh and bind exclusively to either nicotinic or muscarinic receptors can further differentiate the two types. Seven different subtypes of nicotinic receptors have been described in muscle, autonomic ganglia, and central nervous system (CNS) neurons. Five different subtypes of muscarinic receptor also have been distinguished. Acetylcholine is synthesized by all spinal cord and brainstem motoneurons.

In the peripheral nervous system, ACh is the principal transmitter of motor neurons. All alpha and gamma motoneurons release ACh at the neuromuscular junctions. All preganglionic sympathetic and parasympathetic neurons also release Ach. In autonomic ganglia, the primary cholinergic receptors are nicotinic. All postganglionic parasympathetic neurons (and postganglionic sympathetic fibers to sweat glands of the skin) are cholinergic. At these postsynaptic sites, muscarinic receptors predominate.

In the CNS, major concentrations of cholinergic projection neurons are located in two major nuclear clusters referred to as the basal forebrain group and the brainstem tegmental group (*see* **Fig. 15.1**): (1) The basal forebain group comprises magnocellular neurons of the basal nucleus of Meynert, the diagonal band of Broca, and the septal nuclei; (2) the brainstem tegmental group consists of the laterodorsal tegmental nucleus of the central gray and the subjacent pedunculopontine nucleus. The striatum also contains a small number of cholinergic interneurons (Chap. 24). The output from these two groups of nuclei is distributed predominately to neurons with muscarinic receptors.

Roles of the Projections from the Cholinergic Basal Forebrain Group (*see* Fig. 15.1)

The orderly widespread cholinergic projections to the cerebral cortex and hippocampus enhance the responsiveness to inputs of sensory information involved in cognition, attention, learning, and memory. Defects in the cholinergic projections are implicated in the pathophysiology of neuropsychiatric disorders in perinatal development and during aging. A decrease in the density of these axonal terminals is a normal occurrence during aging, as well as degenerative changes in neurons of the frontoparietal cortex and hippocampus and is seen in Alzheimer's disease. The projections to the cingulate gyrus, hippocampus, and amygdala contribute to the functional expressions of the limbic system (Chap. 22).

Roles of Projections from the Cholinergic Brainstem Tegmental Group (*see* Fig. 15.1)

Rostrally directed pathways to the basal ganglia are integrated into the organized motor behavior circuits of the striatopallidal systems, the substantia nigra (pars compacta), and the frontal lobe and also with the cholinergic interneurons of the striatum. Disproportionate activation by cholinergic neurons relative to diminished dopaminergic activation is associated with parkinsonism (Chap. 24). Some rostral connections are links in the functional activity of the reticular activating system, which participates in arousal and wakefulness (Chap. 22). Other cholinergic projections from the pedunculopontine and dorsolateral tegmental nuclei pass into the cerebellum.

Descending cholinergic projections to the lower brainstem core of the pontine and medullary reticular formation have key roles in

sensory processing and autonomic control. Targets include the solitary nucleus, the "medial vasodepressor region" (MDR in **Fig. 20.6**) of the tegmentum, and the vasopressor region of rostroventrolateral reticular nucleus (N.RVL). Cholinergic projections within the reticular formation initiate the rapid eye movement (REM) phase of sleep during which dreaming occurs coupled with a virtual paralysis of somatic body musculature (Chap.20). Projections to the region of the solitary nucleus contribute to the processing of sensory input. Projections to the medial vasodepressor region and to preganglionic sympathetic neurons via the rostral ventrolateral reticular nucleus are involved in cardiovascular control mechanisms (Chap. 20).

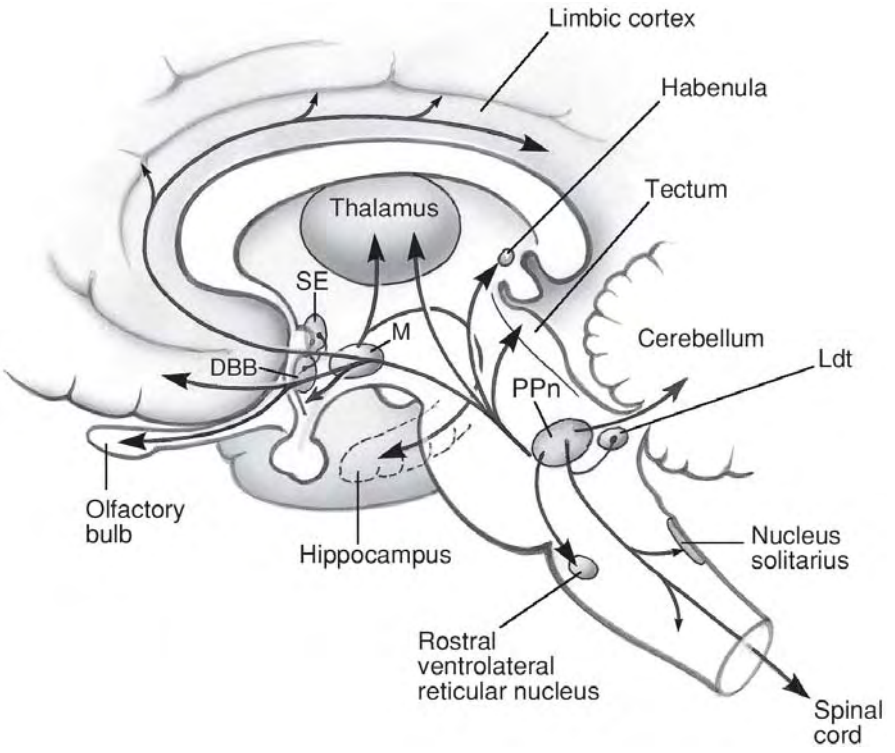


Figure 15.1: Cholinergic pathways. Cholinergic pathways are widely distributed throughout the CNS. Central cholinergic transmission is involved with cognition, attention, memory, and reflex visceral control. A major concentration of cholinergic cells is located in the basal forebrain in the septal nuclei (SE), the diagonal band of Broca (DBB), and the magnocellular part of the basal nucleus of Meynert (M). These nuclei emit extensive orderly cholinergic projections to the frontotemporal lobes and to the hippocampal formation. Subsets of cholinergic cells in the medial septal nuclei and diagonal band of Broca project via the fornix to the hippocampal formation and via the cingulate bundle to the cingulate gyrus of the limbic cortex. A second major group of cholinergic cells is concentrated in the contiguous complex comprised of the lateral dorsal tegmental nucleus (Ldt) and the pedunculopontine nucleus. They project rostrally to the limbic cortex, thalamus, and tectum, posteriorly to the cerebellum, and caudally to the lower brainstem central autonomic core of visceral reflex circuits and to spinal cord sympathetic centers. Visceral reflex circuits, including the solitary nucleus and the rostral ventrolateral reticular nucleus of the medulla, are modulated by acetylcholine, a transmitter that is involved in cardiovascular control along with programmed motor behavior and homeostatic adjustments.

AMINO ACID TRANSMIITTERS

Amino acid transmitters are ubiquitous cellular components of the CNS. Of the known putative transmitters, they are the most numerous and act on the greatest number of synapses. The four designated amino acid transmitters are gamma amino butyric acid (GABA), glycine, glutamate, and aspartate. On the basis of their chemical structure alone, these four are related. GABA acts by opening the chloride channels and thus produces hyperpolarizing currents and inhibitory postsynaptic potentials (IPSPs). Glycine usually exerts inhibitory responses, but it can produce excitatory effects. Glutamate and possibly aspartate act by producing excitatory (depolarizing) postsynaptic potentials (EPSPs). Glutamate always produces EPSPs on ionotropic receptors, whereas activation of metabotropic receptors can produce either excitation or inhibition.

Gamma Amino Butyric Acid

Gamma amino butyric acid (GABA) is widely distributed in inhibitory interneurons and projection neurons of the CNS. GABA is enzymatically converted from glutamate within presynaptic terminals. Following its release and action, GABA is returned via membrane transporter reuptake to provide an additional source for GABA synthesis by the presynaptic neuron. It also enters glial cells for deactivation.

Gamma amino butyric acid, involved in the mechanisms of lateral inhibition, occurs at all levels of the CNS, including but not limited to interneurons of the cerebral cortex, granule cells of the olfactory bulb (Chap. 14), amacrine cells of the retina (Chap. 19), Purkinje cells and basket cells of the cerebellum (Chap. 18), basket cells of the hippocampus (Chap, 22), interneurons and projection neurons of the caudate nucleus and putamen (Chap. 24) and interneurons in the sensory gating, and autonomic control centers in the hypothalamus, reticular formation, and raphe. GABAergic interneurons are critical in the spinal cord, in cardiovascular reflex function and endocrine control, and in the regulation of emotional behavior. The movement disorder *Huntington's disease* is associated with a loss of GABAergic striatal cells, which normally inhibit the globus pallidus and other nuclei of the basal ganglia (Chap. 24).

Distributed throughout the brain, the GABA receptors mediate the sedative effects of benzodiazepines, and the actions of barbiturates. In addition, they appear to be a major site for anesthetic action. Benzodiazepines (e.g., Librium and Valium) are drugs used for alleviating such generalized anxiety disorders as restlessness, difficulty in concentration, and feeling on edge. The effect on specific neurons produced by these drugs results from the enhancement by the action of GABA. The benzodiazepines bind to GABA receptors and, by so doing, enhance the inhibitory effects of GABA by increasing the affinity of the receptors for GABA. The resulting increase in chloride influx through chloride channels acts to reduce anxiety and provide for muscle relaxation.

Glycine

This transmitter, with a restricted distribution in the CNS, is present in interneurons of the spinal cord (Renshaw cells) (*see* **Fig. 3.11**). These neurons exert inhibitory effects by opening the Cl^- channels of the lower motor neurons (Chaps. 3 and 6). In the cerebral cortex, small amounts of glycine have excitatory effects at glutamatergic synapses. By inhibiting the release of glycine, tetanus toxin evokes violent muscle spasms. The blocking of glycine receptors is the likely explanation for the production of muscle spasms following strychnine poisoning.

Glutamate (Glutamic Acid)

Glutamate (glutamic acid) is the most common excitatory transmitter in the central nervous system. Estimates suggest that over one-half of brain synapses release glutamate. It does not readily cross the blood–brain barrier. Glutamate, synthesized within the neuron from glucose, exerts its role by opening Na^+ and K^+

channels. Following its release and action, glutamate is, by uptake, conveyed from the synaptic cleft by membrane transporters either directly to adjacent neurons or into the surrounding glial cells. Within astrocytes, it is enzymatically converted to glutamine, which is released and taken up by transporters into the axonal presynaptic endings, where it is metabolized by the mitochondrial enzyme glutamase back to glutamate. Glutamate supply within presynaptic terminals is continuously replenished by the glutamate–glutamine cycle by the active linkage between neurons (glutamate) and the glia (glutamine).

Glutamate receptors are both ionotropic and metabotropic. (1) There are three types of ionotropic receptor involved in direct gating of ion channels. More than a dozen genes encode subunits of the ionotropic receptors. (2) There are eight metabotropic receptors involved in the indirect gating via G-proteins and second messengers. Thus, like other transmitter systems, glutamate interacts with a variety of receptors.

High concentrations of glutamate synapses are present in the cerebral cortex, dentate gyrus of the hippocampus, striatum, and the spinal cord. Essentially, all of the major efferent projections from the cerebral cortex are components of glutamatergic systems. These comprise the corticobulbar, corticothalamic, corticostriate, and corticopontine pathways. The mossy fibers projecting to the cerebellum also are glutamatergic

The striatum, a major component of the basal ganglia, receives substantial excitatory glutamatergic inputs from all areas of the cerebral cortex (Chap. 24). Suggestions have been made that alterations in the glutamatergic corticostriatal projection system might be one of the initial events leading to the development of Huntington's and other neurodegenerative diseases.

Excitotoxicity by glutamate is the phenomenon by which excess amounts of glutamate destroy neurons. The hyperactivity of excitatory amino acid systems or the failure of normal reuptake mechanisms can be deleterious. These amino acid transmitters, in excess, function as excitotoxins that cause neuronal cell death. Elevated extracellular glutamate concentrations in the CNS have been implicated in neuronal death in head injury, stroke, and epilepsy. Reduced uptake by glial cell glutamate transporters can be an important mechanism underlying excitotoxicity involved in amyotrophic lateral sclerosis (Lou Gehrig's disease).

Aspartate

That aspartate can act as an excitatory amino acid neurotransmitter was first suggested by recorded membrane depolarization of centrally activated neurons and subsequently by involvement of *N-methyl-D-aspartate (NMDA)* glutamate receptors. In recent years, its presence in and release from presynaptic vesicles has been demonstrated, fulfilling the most important criteria for inclusion as a transmitter. Aspartate has been found in many loci, including excitatory nerve terminals of Schaffer collateral–commissural projections in the hippocampus, corticostriate fibers, striatal interneurons, olivocerebellar climbing fiber synapses, dorsal root ganglia, the cochlea and retinal photoreceptors, and bipolar cell terminals. In some hippocampal neurons, aspartate and glutamate are colocalized in the same nerve endings.

BIOGENIC AMINES (MONOAMINES)

The biogenic amines comprise (1) the catecholamines *norepinephrine*, *epinephrine*, and *dopamine* and (2) the indolamine *serotonin (5-hydroxytryptamine [5-HT])*. They are chemical messengers used by neurons as well as by endocrine and other cells. A catecholamine is an organic compound that contains a catechol nucleus and an amino group. Catecholamines are synthesized by neurons of the brain and sympathetic ganglia by a sequence of steps from the essential amino acid tyrosine. The initial and rate-limiting step in this synthesis requires the presence of tyrosine hydroxylase to produce dopamine. In turn, in the presence of dopamine

beta-hydroxylase, dopamine can be converted to norepinephrine, and in the presence of phenlyethanolamine-*N*-methyl-transferace (PNMT) norepinephrine can be converted to epinephrine. Serotonin is synthesized within the neuron in the presence of tryptophan hydroxylase from the amino acid tryptophan.

Reuptake into the presynaptic terminal and enzymatic degradation constrain the fate of the released monoamine neurotransmitters within the synaptic cleft. (1) Reuptake by transporters leads to the recycling of the transmitter into synaptic vesicles of the presynaptic terminals for later release (*see* **Fig. 3.10**). (2) The degradation is accomplished by two enzymes. Catechol-*O*-methyl transferase deactivates transmitters within the synaptic cleft and monoamine oxidase does so on the inside of the presynaptic terminal and on the postsynaptic membrane. These processes are integrated for maintaining a steady supply of transmitters.

Neurons that release norepinephrine and epinephrine are called *adrenergic* neurons; those that release dopamine are called *dopaminergic* neurons; those that release serotonin are called *serotonergic neurons.* The activity of these monoamine transmitters is limited by their reuptake via transporters into the presynaptic ending, where they are recycled into vesicles for future use (Chap. 3). In the human brain, dopaminergic and adrenergic neurons contain melanin pigment and, thus, can often be visualized macroscopically without special stains. These catecholamine cell systems (the solitary tract nucleus and ventrolateral medulla synthesize norepinephrine, designated as the A1-2 and C1-3 cell groups, respectively) communicate stress-related information bidirectionally to specific behavioral, endocrine, and autonomic control centers in the brain and spinal cord.

The major *biogenic pathway systems* in the brainstem are (1) the dopaminergic pathways, originating from the substantia nigra and ventral tegmental area of the midbrain, (2) the noradrenergic pathways, originating from the locus ceruleus and several tegmental nuclei, and (3) the serotonergic pathways, originating from the raphe nuclei (*see* **Figs. 15.2 and 15.3**).

These major modulatory biogenic systems and the cholinergic system have extensive connections encompassing most areas of the brain. Each has a significant role in modulating sensory and motor activities and states of arousal.

Norepinephrine (Noradrenaline) (*see* Fig. 15.2)

In the peripheral nervous system, norepinephrine is synthesized by all postganglionic sympathetic nerves, except those that innervate the sweat glands, which are cholinergic (Chap. 20). Cell groups which synthesize norepinephrine or epinephrine, are located within the pontine and medullary tegmentum (*see* **Fig. 15.2**). The most prominent of these nuclei is the locus ceruleus. Epinephrine neurons (C 3) provide a major source of input to the locus ceruleus. Many of the cells contributing fibers to the tegmental circuitry are not adrenergic. Adrenergic receptors for norepinephrine (mediators of adrenal hormone actions) comprise two groups of metabotropic receptors called alpha- and beta-adrenergic receptors. Each consists of several subgroups coupled to different G-proteins. Of these, the beta-receptors predominate in the brain.

Adrenergic neurons throughout the brainstem are strongly influenced by sensory inputs from somatic and visceral sources and by bodily states and mental-stress-related information. These cells also integrate signals from higher-ordered neural centers and the internal and external milieu from sensory relay nuclei in the dorsal horn of the spinal cord (e.g., stimuli evoking pain), from vagal and glossopharyngeal inputs (e.g., from the carotid sinus, carotid body, and thoracic and abdominal viscera to the nucleus solitarius) (*see* **Fig. 20.5**). These myriads of sensory inputs drive responses generated in the locus ceruleus.

The axons projecting from the locus ceruleus and other adrenergic cells groups of the reticular formation join several pathways: namely the *central tegmental tract,* dorsal longitudinal fasciculus, and the medial forebrain bundle (*see* **Fig. 15.2**). These pathways terminate rostrally in the tectum, thalamus, hypothalamus, hippocam-

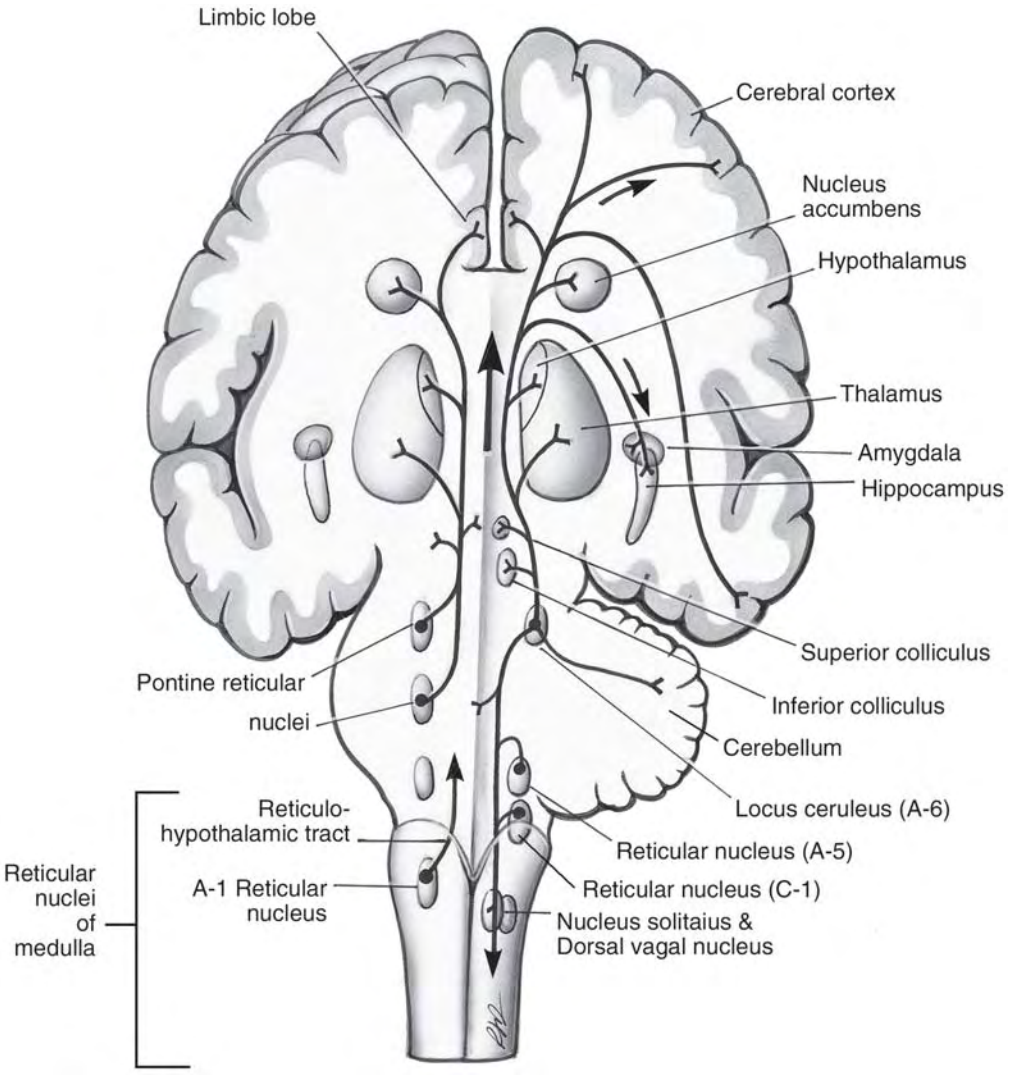


Figure 15.2: Noradrenergic and adrenergic pathways. The ascending pathways on the left originate from medullary and pontine reticular nuclei and terminate in the cerebrum. The ascending A1 noradrenergic pathway terminates in the magnocellular hypothalamus, synapsing with cells that synthesize arginine, vasopressin, and oxytocin; its rostral extension, the C1 adrenergic column, ascends to terminate in the locus ceruleus, amygdaloid nucleus, and parvocellular hypothalamic cells that synthesize corticotrophin-releasing hormone, the visceral thalamus, and preoptic (stress) axis. The descending pathway on the right from A5 norepinephrinergic and C1 adrenergic neurons synapse with thoracolumbar and sacral cholinergic preganglionic motoneurons, and with local A2 and C2 norepinephrine and epinephrine interneurons from local fiber plexuses in the solitary tract. The locus ceruleus (on right) gives rise to widespread noradrenergic projections. Ascending fibers are distributed to the inferior and superior colliculi and continue rostrally into the forebrain. Locus ceruleus efferents in part traveling in the median forebrain bundle terminate in the thalamus, hypothalamus, hippocampus, amygdala, nucleus accumbens, and cerebral cortex. Other fibers project to the cerebellum. Descending fibers go to all levels of the spinal cord and to nuclei in the lower brainstem.

pus, amygdala, and cerebral cortex, dorsally in the cerebellum, and caudally in the lower brainstem and spinal cord.

Locus Ceruleus (LC). The locus ceruleus, located in the upper pons, has the largest collection of norepinephrine neurons (*see* **Fig. 13.14**). In humans, the LC contains about 10,000 neurons on each side, with axons that project to every region of the brain and spinal cord. The "almost universal" distribution of output from the LC is consistent with the belief that the LC acts as a modulator, which sets background tone within the brain. It is the largest source of widespread norepinephrine innervation to the cerebrum. Stimulation of the LC does not yield any well-defined specific effect. Rather, the LC is conceived as having a role in enhancing the signal-to-noise ratio (lateral inhibition) (i.e., suppressing irrelevant stimuli [background noise] and highlighting relevant stimuli). LC projections apparently modify behavioral arousal and cause increased alertness as indicated by electroencephalograms.

The LC is remarkable in that its axons are extensively branched and project directly without interruption until each branch makes synaptic connections through varicosities and synapses in essentially every major region of the CNS. The LC projections are bidirectional, simultaneously influencing widespread central neural activity, behavioral arousal, and sympathetic response patterns. Axons of the LC project (1) rostrally via the central tegmental tract, dorsal longitudinal fasciculus and medial forebrain bundle to the tectum, periventricular hypothalamic, and thalamic nuclei, hippocampus and the cerebral cortex, (2) via the superior cerebellar peduncle to the cerebellum, (3) to many regions of the brainstem, and (4) caudally to the spinal cord (*see* **Fig. 15.2**).

Wide-ranging projection fields of the LC is a feature consistent with its suggested actions as a modulator setting (brain tone) background. The LC is conceived as having the role of suppressing irrelevant stimuli (background noise) and enhancing relevant stimuli. LC projections modulate behavioral arousal, vigilance, and responsiveness to novel, unfamiliar, and surprising stimuli. Thus, the LC influences behavioral arousal and the level of the forebrain and sensory perception (e.g., inputs to the solitary nucleus and the dorsal horn of the spinal cord) and muscle tone.

Epinephrine (Adrenalin) (*see* Figs. 15.2 and 20.5)

Epinephrine is a stress transmitter hormone synthesized on physiological demand by a small number of nuclei in the lower brainstem including in the dorsal vagal complex (solitary nucleus, area postrema, dorsal motor nucleus of the vagus) and the rostral ventrolateral reticular nucleus (n. RVL) (C1 group). Ascending projections go to the norepinephrinergic locus ceruleus, the raphe, amygdala, visceral parts of the thalamus, hypothalamus, septal area, and to the preoptic region. These neurons can exert inhibitory or excitatory influences. The n. RVL sends fibers caudally to the intermediolateral cell column of the thoracolumbar spinal cord, which contains preganglionic sympathetic neurons (Chapter 20). Activation of this pathway increases heart rate and blood pressure, and stimulates release of catecholamines by the adrenal medulla.

Dopamine (*see* Fig. 15.3)

Dopaminergic neurons, wholly confined to the CNS, are concentrated in small groups and give rise to projections generally classified by length as short, intermediate, or long systems, which terminate in discrete targets (*see* **Fig. 15.3**). This is in contrast to the more centralized groups of noradrenergic and serotonergic neurons, which give rise to relatively longer projections to diffuse sites.

Receptors, identified as dopamine receptors, comprise two groups of metabotropic receptor coupled to G-proteins that affect the activity of adenylyl cyclase second-messenger systems. Activation of one subgroup results in excitatory responses and of another in inhibitory responses. A special group functions as autoreceptors that are involved with the reduction of dopamine synthesis and release.

Short Systems. Dopaminergic interneurons wholly confined to the olfactory bulb (granule cells) and retina (amacrine cells) selectively enhance the signal-to-noise ratio by lateral inhibition.

Intermediate-Length Systems. There are three intermediate-length dopaminergic pathways. (1) Tuberohypophyseal projections from the hypothalamus to the anterior and intermediate lobes of the pituitary are involved in

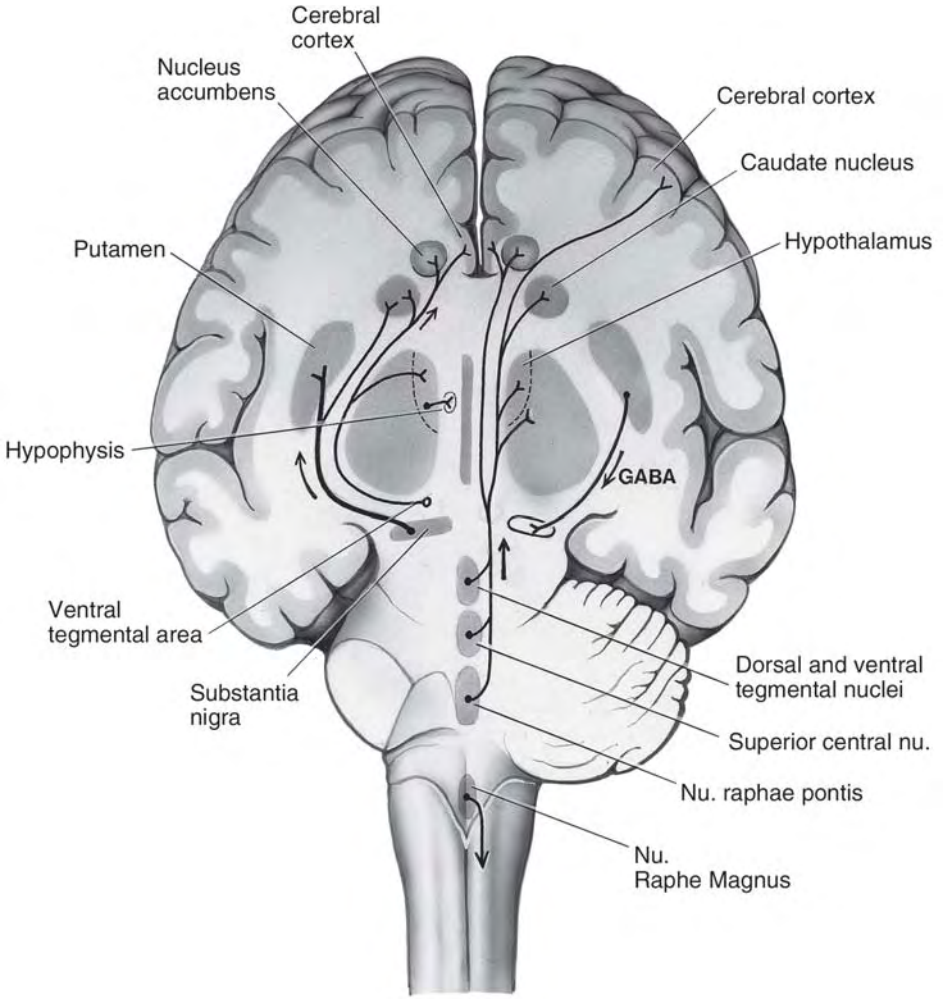


Figure 15.3: Some dopaminergic pathways (left) and the serotonergic pathways (right) are illustrated. The long dopaminergic pathway from the substantia nigra, pars compacta projecting to the putamen, and caudate nucleus is involved in motor control (Chap. 24), whereas that from the ventral tegmental area (VTA) projecting to the nucleus accumbens, amygdala, and hippocampus is involved in emotional responsiveness (Chaps. 22 and 24). One intermediate-length pathway from the hypothalamus to the hypophysis is shown. Reciprocal GABAergic strionigral connections are shown on the right. Serotonergic pathways arise from the raphe. Rostral raphe nuclei send fibers via the medial forebrain bundle to the thalamus, hypothalamus, striatum, and cerebral cortex, particularly the limbic cortex involved in emotions. The nucleus raphe magnus in the medulla projects to the spinal cord and is involved in pain modulation.

inhibiting release of prolactin and melanocyte-stimulating hormone; (2) incertohypothalamic projections from the zona incerta, which is a rostral extension of the brainstem reticular formation, terminate in the hypothalamus; (3) dopamine cells are involved in the regulation of autonomic and endocrine control, release of pituitary hormones, and the expression of sexual and other social behaviors.

Long Systems. The largest groups of dopaminergic neurons in the brain are in the substantia nigra, pars compacta, and the ventral tegmental area (VTA) in the midbrain, which give rise to separate pathways (*see* **Figs. 13.15 and 15.3**). The former emits the *nigrostriatal pathway* to the caudate nucleus and putamen, which has an important role in motor control (Chap. 24). Progressive degeneration of these neurons deprives the striatum of dopamine and causes Parkinson's disease. Neurons of the VTA form the *mesolimbic pathway* to the nucleus accumbens, amygdala, and hippocampus (Chap. 22). This projection is involved in mechanisms of reward; rats choose electrical self-stimulation of the VTA and its dopaminergic neurons over food and sex. The *dopaminergic mesocortical system* from the VTA to neocortex, especially the prefrontal areas, is thought to gate signals that regulate biological drives and motivation associated with initiation of behavioral responses.

Serotonin (5-hydroxytryptamine [5-HT])

Serotonin is synthesized primarily by neurons within the raphe nuclei of the brainstem (*see* **Figs. 9.5 and 15.3**), in mast cells (associated with nociception, Chap. 9), platelets and enterochromaffin cells of the gut (Chap. 20).

Serotonin is synthesized from the amino acid tryptophan and released from synaptic vesicles in axonal endings. Rapid active reuptake by transporters into the same terminal limits the action of serotonin within the synaptic cleft. Enzymatic degradation of serotonin has only a secondary role. Except for one subtype, serotonin receptors are all metabotropic receptors. The numerous serotonin receptor subtypes are grouped into families. All, except one are G-protein coupled with second-messenger pathways.

The raphe nuclei project diffusely throughout the brain and spinal cord. Neurons of the rostral raphe nuclei have axons that ascend in the median forebrain bundle and terminate in the hypothalamus, striatum, cerebral cortex (e.g., limbic cortical areas and primary cortical areas such as primary visual cortex), and the ependyma lining the ventricles. The centrally located pontine and immediately adjacent raphe cell groups innervate the brainstem nuclei of the reticular formation and the cerebellum. The caudal medullary raphe nuclei project to the spinal trigeminal nucleus and to the spinal cord where they terminate in the intermediolateral cell column and also parts of the dorsal and ventral horn.

Serotonergic pathways have a significant role in modulating the responsiveness of the cerebral cortical neurons, in the control of hypothalamic, cardiovascular, and thermoregulatory centers, and in modulating by inhibition afferent input from pain fibers.

The rostral serotonergic projections have active roles in the functioning of the primary sensory cortical areas of the neocortex and in the maintenance of limbic cortical tone for coping with emotion and anxiety. Following its release from mast cells and other damaged cells, serotonin is the agent that activates and sensitizes the nociceptors of the primary "pain" fibers (A-delta and C fibers) (Chap. 9). In the nervous system, serotonin is involved with second-messenger systems as a modulator. The projections to the spinal trigeminal nucleus and dorsal horn of the spinal cord modulate perception of pain, and those to the ventral horn act to regulate tone of the motor system (Chap. 9). In addition, serotonin is involved in a complex of physiologic activities of the hypothalamus, including changes in blood pressure, body temperature, food intake, the sleep–wake cycle, sexual behaviors, certain psychological and psychotic states and responses to certain drugs.

Serotonin reuptake inhibitors such as fluoxetine (Prozac) and a host of more recent agents are widely used to help people cope with a range of behavioral symptoms including mild to severe depression, deficiency in the ability to experience pleasure, fear of rejection, and lack of self-confidence. They act by blocking the serotonin transporter in the axon terminal and the reuptake of serotonin from the synaptic cleft. The result is an increase in the level and duration of the action of serotonin, which is translated in a few weeks into therapeutic effects on both depression and obsessive–compulsive disorders.

NEUROPEPTIDES (NEUROACTIVE PEPTIDES)

The *neuropeptides* comprise the largest class of neuroactive substances, functioning primarily as neuromodulators. They are proteins composed of short chains of 5–50 amino acids. Neuropeptides are synthesized and packaged by fundamentally different mechanisms than utilized for the production of ACh and the biogenic amines. The latter transmitters are produced by the activity of enzymes utilizing molecular precursors delivered to the axon terminals. The polypeptides, from which neuropeptides are derived, are synthesized by an RNA-directed preparation mechanism that produces the precursor neuropeptides *de novo* in the cell body of the neuron through the sequence of ribosomes, endoplasmic reticulum, and Golgi apparatus and finally packaged into vesicles. The initial stages of peptide neurotransmitter processing occur after packaging into vesicles that involve proteolytic cleavage, glycosylation, and disulfide bond formation. The neuropolypeptides packaged in the cell body as large peptide-filled vesicles are transported by axoplasmic flow to the nerve terminals. Neuropeptide synthesis is basically similar to the synthesis of proteins secreted by non-neural glandular cells such as pancreatic enzymes. Unlike the vesicles that contain the biogenic amine small-molecule transmitters, neuropeptide vesicles are not refilled with transmitter by reuptake in the axon terminals. The released neuropeptides are removed from the synaptic cleft via diffusion and degradation by extracellular peptidases. The relatively slow removal of neuropeptides contributes to the longer duration of their effects. Virtually all neuropeptides mediate their effects by activating G-protein-coupled metabotropic receptors and second-messenger slow postsynaptic responses. G-protein receptors comprise many subtypes.

Neuropeptides (peptidergic transmitters) are produced in cells derived from embryonic neural precursor structures (neural plate and neural crest); these include neurons, chromaffin cells of the adrenal medulla, enterochromaffin cells of the gut (Chap. 20), and islet cells of the pancreas.

The neuropeptides found in the brain can be grouped into three major families: (1) *opioid peptides (opiates)* such as enkephalins, endorphins, and dynorphin, (2) *gastrointestinal (gut–brain) peptides* such as vasoactive intestinal polypeptide (VIP), substance P and neurotensin, and (3) *hypophysiotrophic c peptides)* such as vasopressin and oxytocin (Chap. 21).

Vesicles of small-molecule (classical) transmitters in many neurons are colocalized with vesicles of neuropeptides in the axon terminals (*see* **Fig. 15.4**). Two neuropeptides, each in its own vesicles, can also coexist in the same terminal. Some examples of colocalization are ACh with enkephalins, ACh with VIP, GABA with somatostatin, glutamate with substance P, serotonin with substance P, and norepinephrine with enkephalins. The corelease of a fast-acting transmitter with a neuromodulator peptide having a long-lasting effect increases the versatility of synaptic activity. The significance of corelease on the functional activity of the nervous system has yet to be fully evaluated and understood. Evidence indicates that neuropeptides have a role in some aspects of sensing and emotion. They seem to modulate the perception of pain and such aspects of emotion as pleasure and response to stress (Chap. 21).

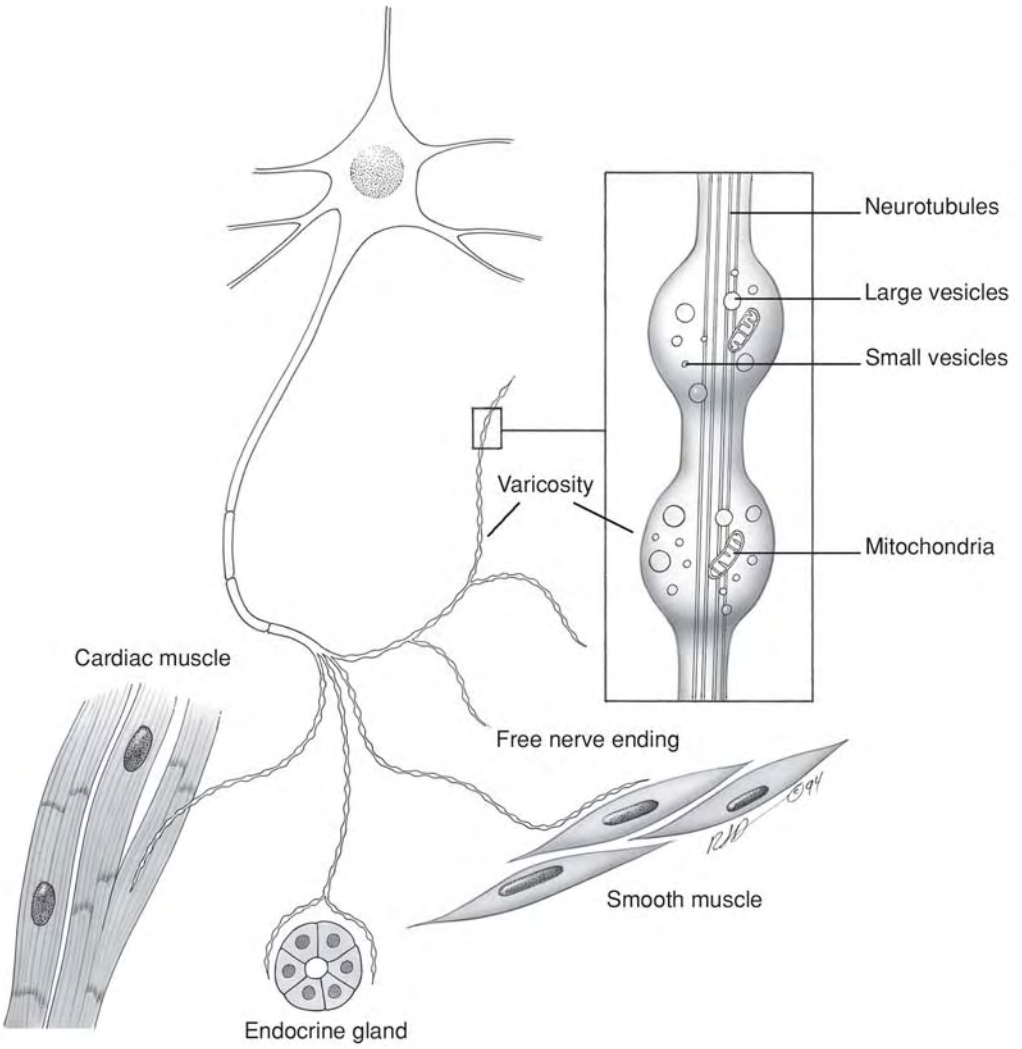


Figure 15.4: Composite illustration of a postganglionic noradrenergic neuron of the sympathetic system. Each varicosity (enlargement) of the axon, called a bouton, contains both large and small vesicles. Neuropeptides are localized in the large vesicles and norepinephrine in the small vesicles. These transmitters, when released, influence the nearby effectors (Chap. 20). The linearly arrayed varicosities along the axon are called boutons en passage and those at the end of the axon are called terminal boutons. Some of the structures innervated are illustrated. The smooth muscle cells are joined together by gap junctions (nexus) to form multicellular functionally integrated units.

The corelease of ACh and VIP by postganglionic parasympathetic fibers innervating the salivary glands illustrates the dual role of these two chemical messengers. Each agent acts on a different target cell. Stimulation of the parasympathetic nerves, which release ACh (contained in small synaptic vesicles), causes increased secretion from the gland and VIP (contained in large vesicles), relaxes smooth muscles of the blood vessels, resulting in vasodilation and increased blood flow through the organ.

Opioid Peptides

Opioid denotes being opiatelike in terms of a functional similarity to morphine (a compound extracted from opium). *Opioid peptides* are endogenous (originating within the body) or synthetic agents that exhibit pharmacological activity similar to morphine. Because the opioid peptides bind with morphine receptors of CNS neurons, they are also called morphinomimetic peptides. Several subtypes of opiate receptor exist, all of which are linked to G-proteins. The endogenous opioids do not cross the blood–brain barrier. Chemical groups of opioid peptides include the *endorphins* and *enkephalins*. *Opiates* are drugs that are derived from the opium poppy. They are used therapeutically as powerful analgesics by binding to opiate receptors.

Endorphins (Endogenous Morphine). The endorphin neurons have cell bodies that are located in the ventral (arcuate area) hypothalamus. Long axons project from these endorphin neurons to the amygdala and to the periventricular region of the thalamus and brainstem, including the raphe nuclei, adjoining reticular formation, and locus ceruleus. The endorphins bind to opioid receptors, which produce analgesia, sedation, and miosis (pupillary constriction). These agents have a central role in controlling the drives for food, water, and sexual activity—all associated with the limbic system (Chap. 22). The effect of opiates in humans is not so much as a specific blunting of pain, but, rather, it is an induced state of indifference or emotional detachment from the experience of distress.

Enkephalins. Enkephalin neurons are widely distributed in the CNS. Each neuron has short axon projections. They are located in the hypothalamus, basal ganglia (globus pallidus and substantia nigra), amygdala and some limbic structures, periaqueductal gray of the midbrain, raphe nuclei, and reticular formation of the brain. Their presence in the spinal nucleus of the trigeminal nerve and the dorsal horn (substantia gelatinosa) of the spinal cord is in regions associated with neurons in the pain pathways (Chap. 9). In some regions, such as the cerebral cortex, there are interneurons containing enkephalins. Enkephalin opioids are believed to reduce sensitivity to pain peripherally (PNS) as well as centrally (CNS) by activating opiate receptors in the periaqueductal gray in the midbrain (increase in enkephalins) (Chap. 9). Morphine and other opiates induce euphoria by activating the receptor sites of the enkephalin neurons of the amygdala and other components of the limbic system. The *dynorphins* are enkephalins that are concentrated in the structures of the limbic system and hypothalamus (Chaps. 21 and 22).

Enkephalin opioids are believed to modulate pain impulses by acting to reduce sensitivity to pain peripherally (PNS) as well as centrally (CNS) by activating opiate receptors in the periaqueductal gray of the midbrain (release of enkephalins) (Chap. 9). Morphine-induced euphoria and the euphoric effects of opiates are presumed to be generated by activating the receptor sites of the enkephalin neurons of the amygdala and structures of the limbic system.

The relief of pain associated with acupuncture treatment results from the release, in the brain, of enkephalins, which bind to opiate receptors. Evidence for this conclusion is that following the administration of *naloxone*, a potent opiate antagonist, the anesthetic effects of acupuncture are blocked. In the placebo effect, pain is often relieved by indifferent medications such as saline. In these cases, the placebo effect can be shown to be blocked by naloxone.

Gastrointestinal (Gut–Brain) Peptides

These peptides were initially identified in the gastrointestinal (GI) tract and were later found in the nervous system.

Secretin/glucogon peptide family, an intestinal acid calcification hormone, is synthesized by the hypothalamic stress axis and cerebellum and is involved in modulating stress adaptation reactions.

Vasoactive intestinal peptide (VIP) is widely distributed in the CNS and in the intrinsic neu-

rons of the gut. It is found in high concentrations in the cerebral cortex, hippocampus, amygdala, and hypothalamus and in the intrinsic neurons of the gut. VIP appears to function as an inhibitory modulator to smooth muscle and as an excitatory modulator of glandular epithelial cells.

Substance P is an excitatory modulator located in the CNS and GI tract. Its effects are of long duration. Its role in the GI tract is to influence the constriction of smooth muscles. Substance P is released in the dorsal horn of the spinal cord by A-delta and C-pain fibers of dorsal root ganglia sensory neurons (Chap. 9). Substance P and GABA are colocalized in specific populations of striatal neurons, which project to the medial segment of the globus pallidus and to the substantia nigra (Chap. 24). Substance P also is found in the raphe nuclei of the brainstem and hypothalamus.

Neurotensin is a gut–brain peptide present in enteric neurons and in the median eminence (hypothalamus), substantia nigra, periaqueductal gray, locus ceruleus, and raphe nuclei. It can participate in the control of body temperature and regulation of the pituitary gland (Chaps. 21 and 22).

Neuropeptide Y (NPY) is widely distributed throughout the endocrine and autonomic regulatory brain regions and the enteric nervous system. Release of NPY in the hypothalamus stimulates food intake, regulates arterial blood pressure, heart rate, and anterior pituitary hormone release and, presumably, enhances memory.

Cholecystokinen (CCK) in humans stimulates gastrointestinal motility, accelerates the transit of food, and stimulates and potentiates actions of pancreatic enzyme secretions and postprandial gallbladder contractions. CCK is a stress factor called on by mental and physical stress and trauma. Its role in the CNS is related to short-term food intake and sensations of satiety and modular nociception.

Hypophysiotrophic Peptides and Other Peptides

Opioid hypothalamic-releasing hormones include *somatostatin*, a peptide that inhibits the release of growth hormone, and *thyrotropin-releasing hormone,* which stimulates the release of thyrotropin from the pituitary gland (Chap. 21).

Neurohypophyseal (Pituitary) Peptide (Hormone)

Vasopressin (antidiuretic hormone) is a neurohypophyseal peptide hormone involved with the reabsorption of water by the kidney and in the constriction of blood vessels.

Oxytocin is a peptide involved in stimulating (1) the smooth muscles of the uterus to contract, (2) milk release in lactating women by the contraction of the myoepithelial cells of the mammary gland, and (3) promoting maternal/infant bonding.

Both vasopressin and oxytocin are synthesized within the cell bodies of hypothalamic neurons of the magnocellular neurosecretory system and stored in the posterior lobe of the pituitary gland (Chap. 21).

NITRIC OXIDE, CARBON MONOXIDE, AND ADENOSINE

Nitric oxide (NO) acts as a neuronal messenger in both the central and peripheral nervous systems. It is an unconventional nitrergic transmitter that is not found in vesicles. Rather, it readily diffuses from its site of origin in the cell through the cell and its membranes. It is possible that NO can be released from both presynaptic and postsynaptic neurons. Note that NO is not the nitrous oxide (N_2O) used as an anesthetic.

In neurons, NO can be produced in response to the excitatory synaptic transmitter glutamate acting through an NMDA receptor that opens Ca^{2+} ion channels. The resulting influx of Ca^{2+} ions passing through the channels bind to the intracellular protein calmodulin that activates the enzyme nitric acid synthase. This enzyme converts the amino acid arginine into nitric oxide. This sequence is rapid, taking only milliseconds. NO is an unstable gas that is extremely membrane permeant. It diffuses

through membranes, bypassing interactions with synaptic membrane receptors. It acts as a modulator in which a postsynaptic neuron can influence a presynaptic neuron. It is extremely labile and lasts for about 5–10 seconds. The mechanisms underlying the actions of NO remain to be elucidated.

Nitric oxide's role in dilating blood vessels (nitrovasodilator) is indicative of one mode of its activity. The parasympathetic neurotransmitter ACh binds to the endothelial cells lining blood vessels to activate the release of NO, which diffuses across membranes to the smooth muscles of a blood vessel (Chap. 20). Nitric oxide causes dilation of the blood vessel as a consequence of the relaxation of the smooth muscle cells. Thus, ACh acts through NO and not directly on the smooth muscles, which lack ACh receptors. Nitric oxide relaxes the muscles through the activation of a second-messenger system involving cyclic guanosine monophosphate, which is related to cAMP (Chap. 3). The dilation is counterbalanced by the sympathetic transmitter norepinephrine, which acts directly with receptor sites on the smooth muscle whose contraction results in constriction of the blood vessel. The NO formed following the absorption of nitroglycerine into the bloodstream relieves the pain symptoms of angina caused by the constricted blood vessels of the heart. Nitric oxide stimulates the cardiac blood vessels to dilate and, thus, restores an adequate blood flow to the heart muscle. NO is released by neurons of the myenteric plexus of the gut as a nonadrenergic–noncholinergic (NANC) agent involved in smooth muscular relaxation during peristalsis (Chap. 20).

The NO released at glutamatergic synapses is thought to have a role in developmental and synaptic plasticity exhibited by neurons (Chap. 3). This can be of significance in the synaptic plasticity underlying learning and memory associated with, for example, the hippocampus (Chap. 22). In addition, NO can participate in the acquisition of learned behavior.

Carbon monoxide is another membrane-permeant gas formed in the brain.

Adenosine (a purine) is a mysterious *purinergic modulator* that is a degradation product of adenosine triphosphate (ATP). This purine acts not only as a chemical messenger, but also, more specifically, as a modulator. Adenosine can exert its influences presynaptically by inhibiting the release of transmitters and postsynaptically by its action on some receptors associated with the second-messenger systems. It is released by sympathetic neurons innervating, for example, the smooth muscles of the vas deferens and the GI tract (*see* Neural Control of the Gut, Chap. 20) and cardiac muscle.

SUGGESTED READINGS

Azmitia EC. Modern views on an ancient chemical: serotonin effects on cell proliferation, maturation, and apoptosis. *Brain Res. Bull.* 2001;56: 413–424.

Azmitia EC. Serotoninergic chemoreceptive neurons: a search for a shared function. *Mol. Intervent.* 2004;4:18–21.

Bredt DS. Nitric oxide signaling specificity—the heart of the problem. *J. Cell. Sci.* 2003;116:9–15.

Burke WJ, Li SW, Zahm DS, et al. Catecholamine monoamine oxidase, a metabolite in adrenergic neurons, is cytotoxic in vivo. *Brain Res.* 2001; 891:218–227.

Cooper J, Bloom F, Roth R. *The Biochemical Basis of Neuropharmacology.* 8th ed. New York: Oxford University Press; 2003.

Davis KL, Dennis Charney D, Coyle JT, Nemeroff C, eds. *Neuropsychopharmacology: The Fifth Generation of Progress.* Baltimore, MD: Lippincott Williams & Wilkins; 2002.

Gundersen V, Chaudhry FA, Bjaalie JG, Fonnum F, Ottersen OP, Storm-Mathisen J. Synaptic vesicular localization and exocytosis of L-aspartate in excitatory nerve terminals: a quantitative immunogold analysis in rat hippocampus. *J. Neurosci.* 1998;18:6059–6070.

Gundersen V, Ottersen OP, Storm-Mathisen J. Aspartate- and glutamate-like immunoreactivities in rat hippocampal slices: depolarization-induced redistribution and effects of precursors. *Eur. J. Neurosci.* 1991;3:1281–1299.

Hall Z, ed. *An Introduction to Molecular Neurobiology.* Sunderland, MA: Sinauer Associates; 1992.

Hardman J, Limbird L, Gilman A. *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* 10th ed. New York: McGraw-Hill Medical; 2001.

Kirchgessner AL. Glutamate in the enteric nervous system. *Curr Opin Pharmacol.* 2001;1:591–596.

Kirchgessner AL. Orexins in the brain–gut axis. *Endocr Rev.* 2002;23:1–15.

Kupfermann I. Functional studies of cotransmission. *Physiol Rev.* 1991;71:683–732.

Myers RD. Neuroactive peptides: unique phases in research on mammalian brain over three decades. *Peptides* 1994;15:367–381.

Nestler EJ, Hyman S, Malenka RC. *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience.* New York: McGraw-Hill Medical; 2001.

Ruggiero DA, Underwood MD, Rice PM, Mann JJ, Arango V. 1999. Corticotropic-releasing hormone and serotonin interact in the human brainstem: behavioral implications. *Neuroscience* 91:1343–1354.

Sabatini BL, Oertner TG, Svoboda K. The life cycle of Ca(2+) ions in dendritic spines. *Neuron* 2002;33:439–452.

Siegel G, Agranoff B, Albers R. *Basic Neurochemistry: Molecular, Cellular and Medical Aspects.* Philadelphia: Lippincott-Raven; 1999.

Snyder SH, Bredt DS. Biological roles of nitric oxide. *Sci. Am.* 1992;266:68–70.

Strand F. *Neuropeptides: Regulators of Physiological Processes.* Cambridge, MA: MIT Press; 1999.

Tong Q, Kirchgessner AL. Localization and function of metabotropic glutamate receptor 8 in the enteric nervous system. *Am. J. Physiol. Gastrointest. Liver Physiol.* 2003;285:G992–G1003.

16
Auditory and Vestibular Systems

The Labyrinths
Auditory System
Vestibular System

The auditory system is exteroceptive and concerned with perception of sound. The vestibular system, in contrast, is proprioceptive and concerned with the maintenance of equilibrium and orientation of the body in space and, hence, involved in motor activities. The receptors (mechanoreceptors) are hair cells located within specialized neuroepithelial structures. They are responsible for converting mechanical energy in the form of displacement of their surface elements caused by sound waves (for hearing) and head movements (for balance) into electrochemical energy to be transmitted to the auditory (cochlear) or vestibular root of the vestibulocochlear nerve (cranial n.VIII), respectively. The hair cells are located within the membranous labyrinth of the inner ear, which is a closed tubular system filled with endolymph. The auditory hair cells are in the spiral organ of Corti in the cochlea. The vestibular hair cells are located in the macula of the utricle, the macula of the saccule, and the cristae ampullares of the three semicircular canals. The cochlear and vestibular nerves merge to form the vestibulocochlear nerve or eighth cranial nerve, which enters the brainstem at the *cerebellopontine angle* (junction between the cerebellum, pons and medulla; *see* **Fig. 13.11**).

THE LABYRINTHS

There are two labyrinths: an osseous (or bony) labyrinth and a membranous labyrinth. The *osseous labyrinth*, a network of canals and vesicles located within the temporal bone, forms the bony framework for the cochlea, vestibule (utricle and saccule), and three semicircular canals (*see* **Fig. 16.1**). The *membranous labyrinth* is enclosed within the osseous labyrinth—analogous to a tube within a tube (*see* **Fig. 16.2**). The hair cells are located within the membranous labyrinth. The space within the osseous labyrinth (perilymphatic space), which surrounds the membranous labyrinth, is filled with *perilymph*; the space within the membranous labyrinth (endolymphatic space) is filled with *endolymph*. The hair cells are located within the endolymphatic space. The endolymphatic and perilymphatic spaces are separate compartments. Their respective fluids have different chemical compositions similar to the differences between an extracellular fluid (perilymph) and intracellular fluid (endolymph). Thus, they have different resting potentials allowing for the passage of charge and stimulation of the hair cells.

Osseous Labyrinth

The osseous labyrinth, located within the petrous portion of the temporal bone, consists of the vestibule, semicircular canals, and cochlea. It develops from the primitive otic capsule. The utricle and saccule, constituents of the membranous labyrinth, are within the vestibule. Openings into the vestibule include the vestibular aqueduct, foramina for the passage of vestibular nerve bundles, and the oval window. The three semicircular canals surround the semicircular ducts. The bony cochlea is a spiral structure that winds two and a half

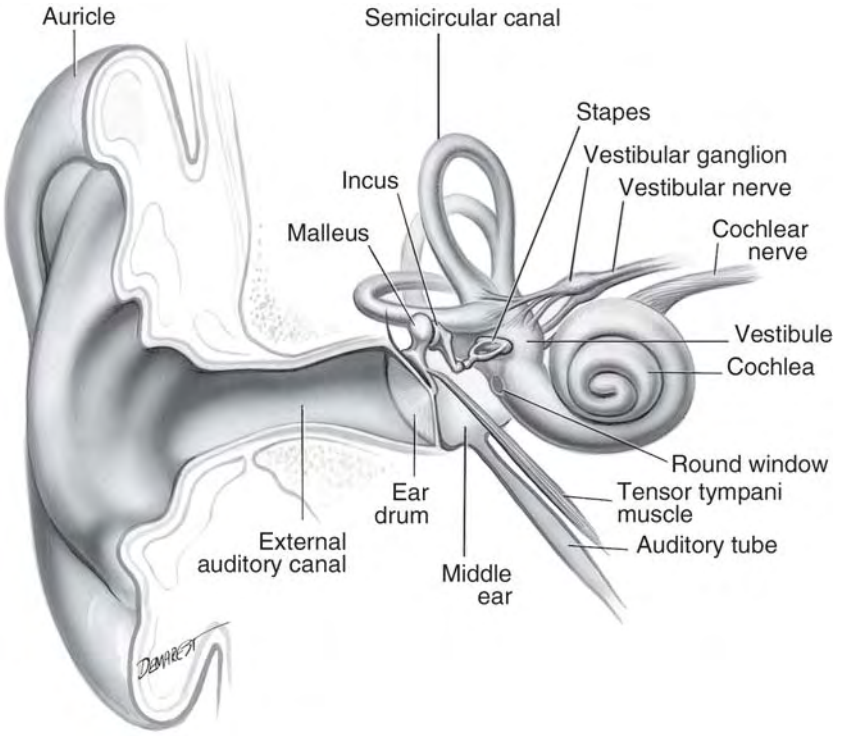


Figure 16.1: External ear, middle ear, and inner ear on right side viewed from the front.

turns from base to apex around a bony core, the *modiolus,* which contains the cell bodies (spiral ganglion) of the afferent auditory nerve fibers as well as efferent fibers from the brainstem that go to the auditory hair cells. The cochlea portion of the osseous labyrinth is divided into the *scala vestibuli* and *scala tympani,* which are separated from each other, except at the apex, by the membranous labyrinth (cochlear duct, scala media). The scala vestibuli and scala tympani communicate at the apex of the cochlea through a small opening called the *helicotrema*. The scala vestibuli is in continuity with the perilymphatic space of the vestibule, where the oval window is located, sealed with the stapes foot-plate. An opening at the basal end of the scala tympani, sealed by a connective tissue membrane, is called the round window. It should be noted that the perilymphatic space is connected through the narrow cochlear aqueduct at the basal end of the scala tympani to the subarachnoid space. Perilymph is therefore in continuity with cerebrospinal fluid.

Membranous Labyrinth

The vestibular portion of the membranous labyrinth on each side consists of (1) three semicircular ducts, lateral (or horizontal, actually tilted with the front higher by 30°), superior (or anterior), and posterior (or inferior), named for their orientation within the temporal bone, (2) the utricle, and (3) the saccule. The three semicircular ducts are in open communication with the utricle via five openings. Each semicircular duct has one bulbous portion, the ampulla. The nonampullated ends of the superior and posterior canals are joined together. The *cochlear duct* or *scala media* is the portion of the membranous labyrinth associated with the auditory system (*see* **Figs. 16.2 and 16.3**). The cochlear duct is connected to the saccule via the *ductus reuniens*. The utricular duct (from the utricle)

and the saccular duct (from the saccule) merge to form the *endolymphatic duct* (within the bony vestibular aqueduct), which conveys endolymph to the *endolymphatic sac* (*see* **Fig. 16.2**). The endolymphatic sac, located between layers of a well-vascularized region of the dura mater on the posterior face of the petrous bone, is where endolymph is cleared from the membranous labyrinth into the venous system and perilymph is drained into the subarachnoid space from the osseous labyrinth. The membranous labyrinth overlying the apical end of the receptor cells (cochlear duct, saccule, utricle, semicircular ducts, and endolymphatic duct and sac) is filled with endolymph, which is actively formed in both the cochlear and vestibular portions of the labyrinth. The receptors (hair cells) have tight junctions along the apex that block endolymph from reaching basal portions of the cells, which are bathed in perilymph.

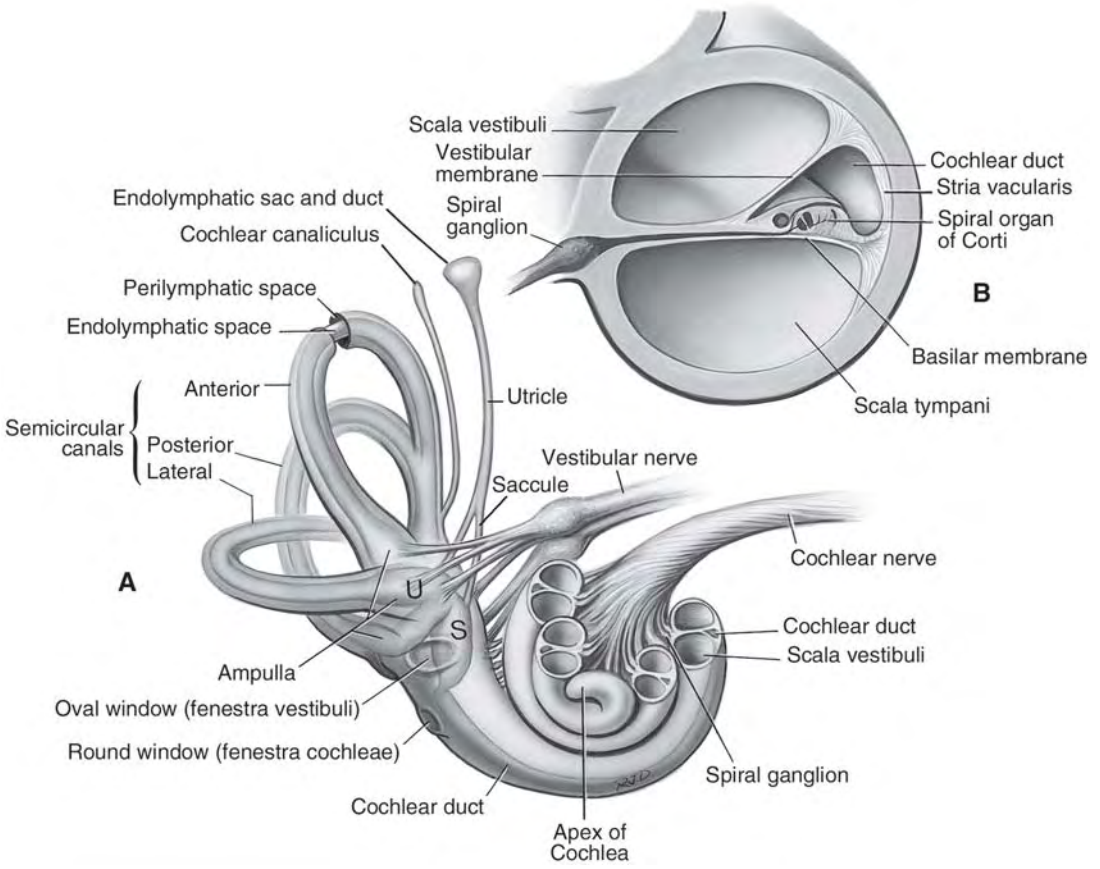


Figure 16.2: The labyrinth. **(A)** Right labyrinth, from the front. The perilymphatic space is located between the bony labyrinth and the membranous labyrinth: it extends as the cochlear canaliculus. The endolymphatic space is located within the membranous labyrinth, which includes the three semicircular ducts, utricle, saccule, cochlear duct and endolymphatic duct and sac. **(B)** Cross-section through a half-turn of the cochlea. The scala vestibuli and scala tympani (containing the perilymph) are connected at the apex of the cochlea through a narrow opening called the helicotrema (not shown).

Sensory Receptor Areas

There are six specialized areas within the membranous labyrinth on each side that contain sensory epithelial receptors (hair cells) in contact with the terminal endings of the eighth cranial nerve: three cristae ampullares (one in the ampulla of each semicircular duct), one macula utriculi, and one macula sacculi, all innervated by vestibular neurons and the spiral organ of Corti in the cochlea, innervated by auditory neurons. The organ of Corti is located within the cochlear duct (scala media) of the membranous labyrinth.

AUDITORY SYSTEM

Ear Anatomy and Physiology

The "ear" consists of the external ear, middle ear, and inner ear (*see* **Fig. 16.1**).

The external ear (auricle and external auditory meatus) is separated from the middle ear by the *tympanic membrane* (ear drum). The external auditory meatus functions as a sound resonator, increasing the sound pressure level (usually measured in decibels) at the tympanic membrane. The auricle and head have baffle

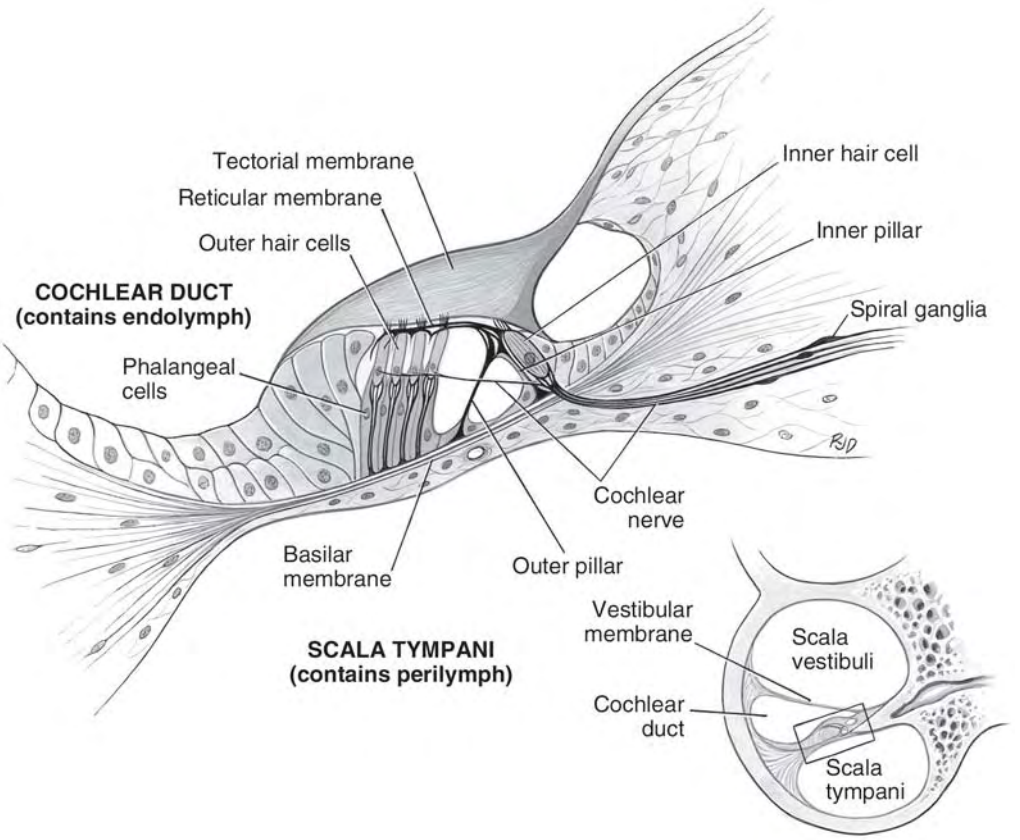


Figure 16.3: The organ of Corti in the middle turn of the cochlea with four rows of outer hair cells; there are three rows in the basal turn and five in the apical half-turn, reflecting the fact that the basilar membrane is wider at the apex. Inner and outer pillar cells enclose the tunnel of Corti, which contains perilymph and is traversed by cochlear nerve fibers. The pillars have fenestrated stiff processes that cover the apical surface of the hair cells.

and shadow effects on sound waves that aid in sound localization.

The middle ear is an air-filled space bounded laterally by the tympanic membrane and medially by the inner ear. A chain of three ear ossicles traverses this space: the *malleus,* which is attached to the tympanic membrane; the *incus* in an intermediate position; and the *stapes,* whose foot-plate is inserted into the *oval window*. Two small skeletal muscles are in the middle ear: the *tensor tympani* inserted into the malleus and the *stapedius*, which is attached to the stapes. The latter is responsible for the stapedial or acoustic reflex. The middle ear functions as a mismatch transformer increasing the sound pressure level at the oval window as compared to that at the tympanic membrane. This is necessary because of the increased impedance of the cochlear fluids (perilymph) as compared to air in the external auditory canal. A greater amount of pressure is necessary to vibrate the higher-impedance fluid. If the tympanic membrane and ossicular chain were not present, sound waves would hit the oval and round windows simultaneously, canceling out their vibrations. Also, there would be insufficient energy to adequately stimulate the inner ear. This is important clinically in patients with chronic middle ear disease.

The narrow auditory (eustachian) tube connects the middle ear with the nasopharynx. It is important for equalizing air pressure on the two sides of the eardrum.

The inner ear is the cochlea (spiral shell). Traveling waves within the perilymph, generated by movement of the stapes in the oval window, displace the basilar membrane together with the organ of Corti containing the specialized auditory receptors—the hair cells.

Sound Reception

Vibrations can be perceived as sounds. Sound travels in the form of waves with a characteristic frequency, measured in hertz (Hz) (cycles per second) and amplitude, measured in sound pressure level (decibels [dB]). Frequency is a measure of pitch, and amplitude is a measure of loudness. It is important to remember that the decibel scale is logarithmic, so a 10-dB increase in intensity has 100 times more energy. Zero decibels is the average threshold for human hearing and 140 dB is the threshold for pain. Normal conversational speech is 40–60 dB. Frequencies between 50 and 20,000 Hz can be detected as sound. The frequencies perceived with optimum acuity by most subjects fall between 2000 and 5000 Hz. Airborne vibrations (sound waves) pass through the external auditory meatus and set the tympanic membrane vibrating (air conduction). Some vibrations can bypass the ear ossicles and reach the perilymph directly through bone (bone conduction). The oscillations of the stapes footplate in the oval window produce pressure waves within the perilymph of the scala vestibuli that travel variable distances, depending on frequency, up the $2^1/_2$ turns (approximately 35 mm) of cochlea (*see* **Fig. 16.2**). High-frequency waves press down maximally on the basilar membrane near the base of the cochlea, whereas lower-frequency waves impinge progressively toward the apex. Thus, each section of the basilar membrane has a characteristic tuning curve for which it is most sensitive (this is found in all levels of the auditory system). The waves cause downward, followed by upward, deflections of the basilar membrane. To allow propagation of the pressure (traveling) waves in the inner ear, the membrane of the round window bulges outward and inward in synchrony (equal and opposite) with movement of the stapes. This is necessary because perilymphatic fluid is incompressible within the bony cochlea; traveling waves would not be generated if there were no compensatory movements at the round window.

Cochlear Duct (Scala Media)

The *vestibular (Reissner's) membrane* forms the roof of the scala media and separates it from the scala vestibuli. This membrane is a single layer of cells that runs obliquely from the upper limit of the spiral ligament (attached to the lateral wall of the cochlea) to the limbus on the osseous spiral lamina. The *basilar membrane*, bordering the scala tympani, forms the floor of

the scala media; it is suspended between the osseous spiral lamina and the lower extent of the spiral ligament. The spiral *organ of Corti*, containing the auditory receptors, rests on the basilar membrane. The lateral wall of the scala media is formed by the stria vascularis on the spiral ligament. It contains specialized cells for active transport of ions to maintain the +80-mV endolymphatic potential; thus, the current necessary for hair cell depolarization.

The Organ of Corti and Auditory Hair Cells

The spiral organ of Corti has two types of hair cell: flask-shaped inner and cylindrical outer (*see* **Figs. 16.3 to 16.5**). There is a single row of *inner hair cells* and between three (at the base) and five (at the apex where the basilar membrane is wider) rows of *outer hair cells* for a total of about 15,500. The inner and outer hair cells are separated by the tunnel of Corti. Both have efferent as well as afferent nerve endings. However, direct efferent innervation goes only to the outer hair cells. Efferents to the inner hair cells synapse on the afferent fibers. Roughly 95% of the bipolar cells in the spiral ganglion supply afferent innervation selectively to the inner hair cells. Each innervates only 1 inner hair cell, which, in contrast, is

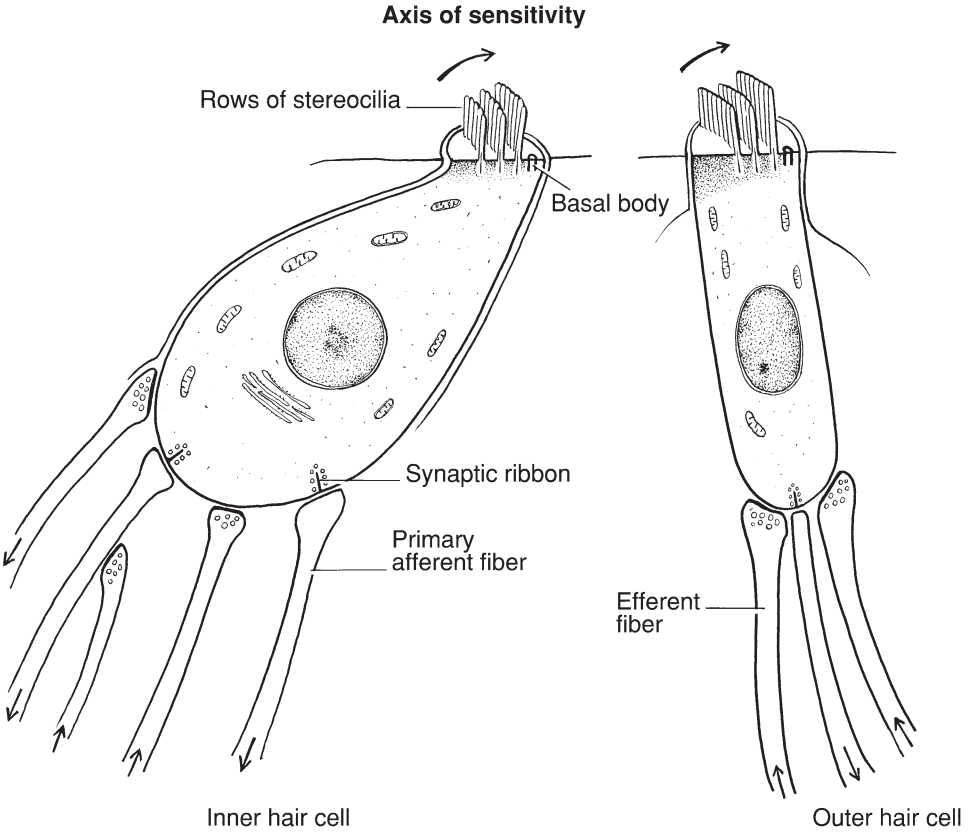


Figure 16.4: The hair cells of the organ of Corti. The axis of sensitivity of a cochlear hair cell is bending of the stereocilia in the direction of the basal body. Flask-shaped inner hair cells receive afferent innervation from 95% of the cochlear nerve fibers. Cylindrical outer hair cells have a scant afferent innervation, but a greater efferent innervation from neurons in the brainstem. They change the characteristics of the basilar membrane. Efferents to the inner hair cells synapse on the afferent fibers. Inner hair cells are responsible for all auditory sensations.

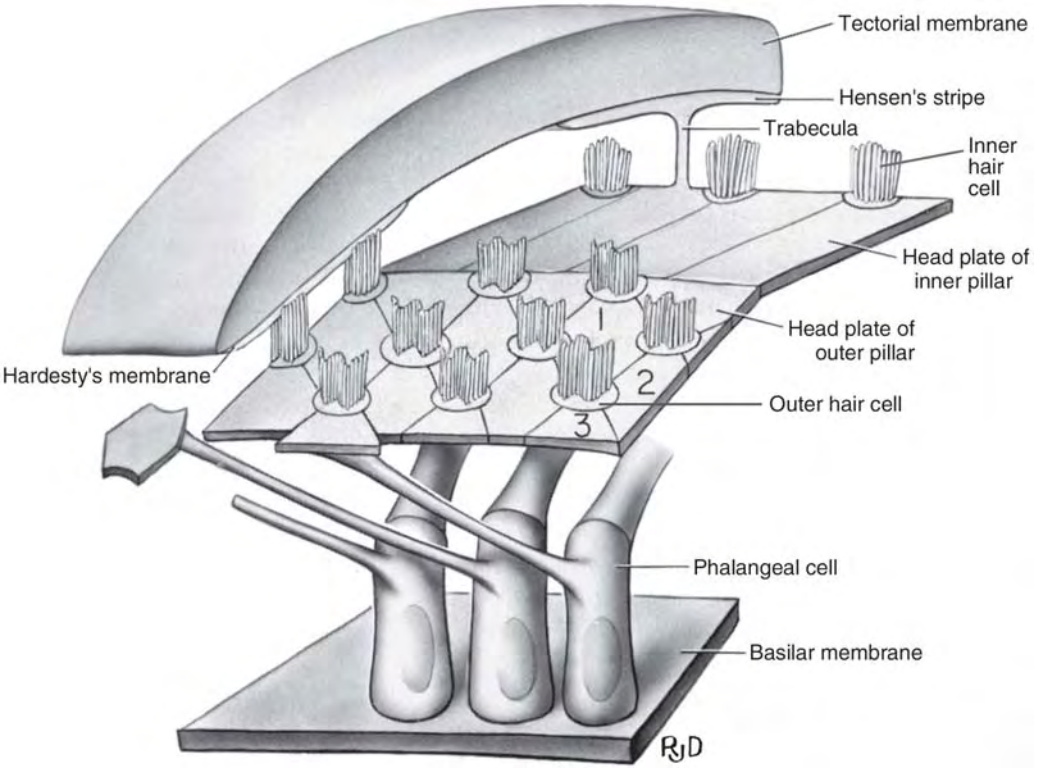


Figure 16.5: Drawing of the organ of Corti viewed from the outer rim of the tectorial membrane. Stereocilia extend from the apical side of hair cells through the stiff reticular membrane, composed of processes (1, 2, 3) of phalangeal cells together with the head plates of inner and outer pillar cells, and are embedded in the tectorial membrane. (From Rivera-Dominquez, et al, 1974.)

connected to axons of as many as 10 ganglion cells. Auditory perception is attributed exclusively to this type cell. The outer hair cells are contractile, and by changing length, they alter the tension on the basilar membrane, thereby maximizing the responsiveness of the inner hair cells to the appropriate frequencies.

The distinctive feature of the hair cells is several rows of *stereocilia* (actually microvilli) called a hair bundle extending from the apical surface (*see* **Fig. 16.4 and 16.5**). The stereocilia become progressively longer toward the outer end of the cell. The *basal body*, the base of a degenerated kinocilium, is located adjacent to the tallest row of stereocilia. All hair cells are polarized with the basal body located at the edge furthest from the modiolus. The stereocilia protrude through a rigid reticular lamina, with their distal tips embedded in the gelatinous *tectorial membrane* (*see* **Figs. 16.3 and 16.5**). There are as many as several hundred stereocilia on each of the 3500 inner hair cells and 12,000 outer hair cells in the human organ of Corti (*see* **Fig. 16.5**). With displacement of the basilar membrane, a shearing force is produced with an accompanying bending of the stereocilia that results because the tectorial membrane has a different fulcrum and does not move to the same degree as the hair cells. The hair cells are polarized, with depolarization occurring when the cilia are bent along the axis of sensitivity (i.e., toward the basal body) (*see* **Fig. 16.4**). The hair cells act both as transducers (converting mechanical energy into electro-

chemical energy) and biologic amplifiers. The organ of Corti is a frequency analyzer, with the highest pitches mediated at the base of the coil, the lowest at the apex, and intermediate pitches in an organized topographic pattern between the highest and the lowest (*tonotopic organization*). In addition to different frequencies causing maximum displacement of the basilar membrane at given points, the hair cells themselves have variable mechanical and electrical properties: (1) the length of the hair bundle increases from base to apex of the cochlea, just as piano strings become longer toward the low-frequency end, and (2) the membrane potential resonates at different frequencies along the length of the organ of Corti. Perception of loudness is related to the amplitude of the displacement of the basilar membrane: Louder sounds activate more hair cells.

Hair cells at rest have a basal rate of electrical activity or steady-state potential. Potassium-gated ion channels at the tips of the stereocilia are opened or closed by tip links, which connect adjoining stereocilia. At rest, some channels are open and others closed. With displacement of the stereocilia toward the basal body, gates are preferentially opened. Although potassium conductance usually has a hyperpolarizing effect, because endolymph, unlike other extracellular fluids, has a high K^+ concentration, K^+ enters the cell, causing depolarization (the generator potential). This opens voltage-gated calcium channels; entry of Ca^{2+} triggers transmitter release at the base of the hair cell, where synaptic contact is made with first-order nerve endings. Thus, each hair cell is a mechanoreceptor that transduces mechanical energy of the sound waves into graded potentials, which in turn stimulate the nerve endings of the bipolar cells of the spiral ganglion of the cochlear nerve.

Ascending Pathways (*see* Fig. 16.6)

The approximately 30,000 neurons of the cochlear nerve have (1) distal branches that terminate on both inner and outer hair cells, but primarily the former, and (2) proximal branches that synapse on many neurons in the cochlear nuclear complex (dorsal, posteroventral, and anteroventral cochlear nuclei) located on the posterolateral surface of the upper medulla (*see* **Fig. 13.11**). Each subdivision is tonotopically organized (has a frequency specific tuning curve) and gives rise to at least partially separate second-order ascending fiber systems. Most fibers decussate in the caudal pons and ascend in the contralateral lateral lemniscus; a smaller number ascend ipsilaterally. The great majority of second-order fibers arise from the anteroventral cochlear nuclei and cross to the opposite side in the rather conspicuous trapezoid body in the anterior pontine tegmentum; a large number terminate in the superior olivary complex on both sides. Fibers from the posteroventral and dorsal cochlear nuclei decussate more posteriorly in the pontine tegmentum as the intermediate and dorsal acoustic striae, respectively. Fibers in the former partially terminate in parts of the superior olivary complex "periolivary nuclei" that give rise to the olivocochlear bundle, which synapses on the receptor cells; fibers of the dorsal acoustic stria mainly bypass the superior olivary complex.

Superior Olivary Complex and Localization of Sound. The major nuclei of the superior olivary complex are the lateral (SOL) and medial (SOM) superior olivary nuclei. Other components in humans include several periolivary cell groups. In order to localize sounds, cues arriving at the two ears must be compared. Binaural interaction first occurs at the level of the superior olivary complex. There are different mechanisms for localizing high- and low-frequency sounds. At high frequencies, the head casts a sound shadow, producing differences in the intensity of signals reaching the two ears. This disparity is analyzed in the SOL; the anteroventral cochlear nucleus excites the ipsilateral SOL and inhibits the contralateral SOL via fibers that cross in the trapezoid body. At low frequencies (below about 3000 Hz), the SOM compares time and phase differences of signals arriving from the anteroventral cochlear nuclei to localize a sound source. In addition to a

sound arriving at the two ears at slightly different times, fibers from the anteroventral cochlear nucleus to the ipsilateral SOM travel a shorter distance than do the fibers terminating on the same nucleus from the opposite side.

Higher Levels of the Auditory Pathway. Several nuclei are intercalated within the ascending auditory pathways to the auditory cortex; these include the superior olivary complex, nuclei of the lateral lemniscus, inferior colliculus, and medial geniculate body. Commissural fibers interconnect the nuclei of the lateral lemniscus and inferior colliculi. The portion of the lateral lemniscus between the inferior colliculus and the medial geniculate body is called the brachium of the inferior colliculus. Fibers taking origin from the medial geniculate body enter the posterior limb of the internal capsule (sublenticular portion) and continue as the auditory radiations to the transverse gyri of Heschl (areas 41 and 42) on the floor of the lateral fissure in the temporal lobe (*see* **Fig. 25.5**). Data suggest that the cortex involved in auditory processing includes the entire superior temporal gyrus as well as portions of the parietal, prefrontal, and limbic lobes. The two hemispheres are interconnected via the corpus callosum.

The complexity of the auditory cortex is revealed in studies indicating that it consists of a tonotopically organized primary cortex (area 41) in the temporal lobe and at least five other tonotopically organized auditory cortical areas in the immediate vicinity of the primary auditory cortex.

Two functionally significant features of the ascending pathways should be emphasized:

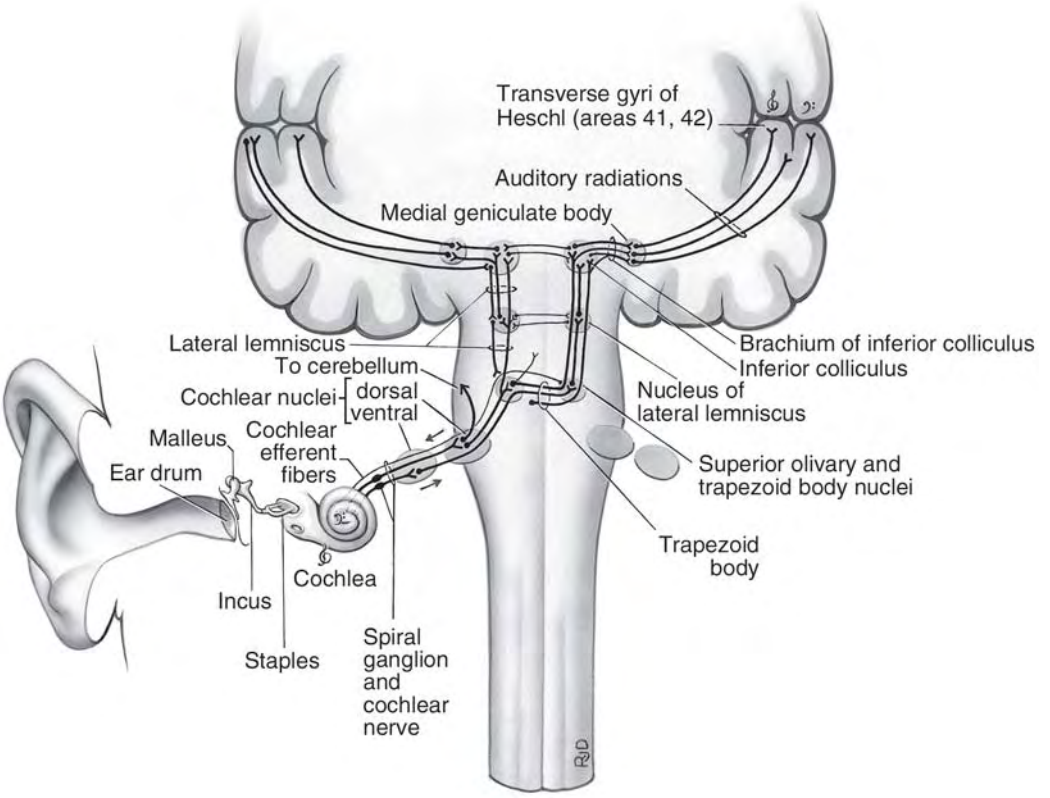


Figure 16.6: Diagram of the auditory pathways from one cochlea.

(1) the processing centers at each level have a multiple tonotopic organization and (2) the output from each ear is conveyed bilaterally, i.e., via auditory pathways of both sides, with a stronger contralateral projection.

Descending Pathways

Descending fibers, which accompany the ascending fibers, project downstream from auditory cortex and the other nuclei of the auditory pathway. They have a role in processing ascending information, enhance signals, and suppress noise. This possibly is related to localizing functions of the superior olivary complex, enabling a listener to focus on a particular speaker and inhibit other voices. Fibers from periolivary portions of the superior olivary complex are integrated into a feedback system that courses as crossed and uncrossed projections (called the olivocochlear or cochlear efferent bundle) via the vestibulocochlear nerve, before terminating at the base of the outer hair cells and at the distal end of afferent fibers that innervate inner hair cells, in the organ of Corti. The inhibitory influences conveyed by these efferents act to suppress the activity of the afferent fibers of the cochlear nerve and to fine-tune the basilar membrane through action of the outer hair cells.

Functional and Clinical Considerations

Deafness restricted to one ear is usually associated with damage to the cochlear nerve or the cochlea itself (sensorineural hearing loss [SNHL]) or the conducting apparatus within the middle ear (conductive hearing loss) on the side of the deafness. Unilateral lesions of the ascending auditory pathways above the level of the cochlear nuclei produce only minor perceptual impairments because of the strong bilaterality of the pathway. Evidence indicates that unilateral lesions do cause impairments in localizing ability, which also is severely disturbed by lesions involving the trapezoid body. Bilateral lesions of the central auditory pathway are rare because the tracts and nuclei are far apart, near the lateral margin of the brainstem; the auditory cortex similarly occupies a region at the lateral margin of the cerebrum. Evidence from animal studies indicates that the auditory cortex is not essential for discrimination of intensities or frequencies, but is necessary for differentiation of more complex functions such as patterns or rhythms.

An irritative lesion of the organ of Corti or the cochlear nerve can result in *tinnitus* (the subjective hearing of hissing, roaring, buzzing, and humming sounds). This can occur in acoustic neuromas of n.VIII in the cerebellopontine angle. Tinnitus can be followed by nerve deafness as the irritative lesion expands and all cochlear nerve fibers are interrupted. Nerve deafness is also associated with occlusion of the internal auditory artery, aging, and Meniere's disease (*see* later).

Several commonly used drugs are ototoxic. The most common drugs to cause irreversible SNHL are the aminoglycosides, such as gentamicin. Early cessation of treatment will allow reversal of the damage. This class of antibiotic causes direct hair cell toxicity to both the auditory and vestibular hair cells. This is usually an unwanted side effect of aminoglycoside use, but in patients with severe vertigo, it is used to alleviate symptoms. Other common agents that cause ototoxicity include the loop diuretics, which cause both permanent and reversible losses, and salicylates, including aspirin, which cause a reversible hearing loss. Cisplatin, a common antineoplastic agent, causes a permanent hearing loss. An early symptom of ototoxicity from all of these agents is often tinnitus.

Damage to the eardrum and the ossicles of the middle ear is usually followed by a partial deafness. This middle-ear deafness (conduction deafness in otosclerosis) is accompanied by a partial loss in the perception of low-pitched sounds and a mild loss in the entire auditory range.

Presbycusis is the gradual impairment of ability to perceive or discriminate sounds in old age. This increasing difficulty in hearing high-pitched sound is associated with degeneration of the hair cells near the base of the cochlear coil. Conduction deafness can occur as a consequence of middle-ear disease such as otitis

media. A tuning-fork test, the Rinne test, can be used to distinguish bone-conduction deafness from air-conduction deafness. The base of a vibrating tuning fork is applied to the mastoid process of the skull and sound is heard by bone conduction; at the moment the sound ceases, the vibrating fork is placed near the external auditory meatus. A subject with normal hearing will hear the vibrations by air conduction after the bone-conduction hearing ceases. In middle-ear deafness, the vibrating fork cannot be heard by air conduction. In partial nerve deafness, air-conduction hearing is better than bone-conduction hearing, although both are diminished.

Cochlear Implants. Implantation of multiple-array electrodes into the cochlea in cases with nonfunctional hair cells has become relatively commonplace. The electrodes, which electrically stimulate the fibers of the eighth nerve, receive coded signals that are transmitted transcutaneously from a speech processor connected to a small microphone positioned behind the ear.

Brainstem Auditory Evoked Potentials. Evoked potentials are employed for diagnostic purposes. They are recorded from electrodes applied to the scalp utilizing a computer to average multiple responses. Potentials from the various portions of the auditory pathway have different latencies and characteristics of waveform. Abnormalities in the potentials can be used to differentiate between conductive and sensorineural hearing loss and to aid in determining the presence and location of injury to the auditory pathways, as in multiple sclerosis, strokes, tumors, and so forth.

Middle-Ear Reflex. The middle-ear reflex (contraction of the stapedius and tensor tympani muscles) is activated by loud sounds above about 80 dB. This dampens the amplitude of movement of the ear ossicles and of the oscillations of the stapes in the oval window, thus protecting the organ of Corti from damage. Under normal physiological conditions, loud sounds are perceived as less intense than would be shown on a meter that measures decibels. When the reflex is deactivated, hyperacusis occurs and loud sounds appear louder. This phenomenon occurs in facial nerve palsies as a result of paralysis of the stapedius muscle innervated by this nerve (Chap. 14). Although the tensor tympani also contracts and increases tension on the eardrum, lesions of the trigeminal nerve do not elicit hyperacusis. Hyperacusis is defined as an increased sensitivity to sound. A small number of people with otherwise normal hearing, including the middle-ear reflex, experience hyperacusis to sounds of all intensities, particularly high frequencies. This can be quite disruptive. It sometimes accompanies migraine headaches. The cochlear nerve acts as the sensory limb of the reflex arc. The cochlear nuclei send fibers to motor neurons in the region of the superior olivary complex adjacent to the facial nucleus that project via the facial nerve to the stapedius.

Other auditory reflexes involve various brainstem nuclei and their projections to the spinal cord, especially to the motor centers innervating the neck musculature, which rotates the head in the direction of the source of the sound.

VESTIBULAR SYSTEM

The purpose of the vestibular system is to signal changes in the motion of the head (kinetic) and in the position of the head with respect to gravity (static). The information from the periphery required by the nervous system to perform these roles is obtained from three afferent sources: the eyes, general proprioceptive receptors throughout the body, and the vestibular receptors in the inner ear. These three afferent sources are integrated into three systems (visual, proprioceptive and vestibular systems) known as the equilibrial triad.

The vestibular system is a special proprioceptive system that functions to maintain equilibrium, to direct the gaze of the eyes, and to preserve a constant plane of vision (head position), primarily by modifying muscle tone.

The Utricle, Saccule, Cristae Ampullares, and Vestibular Hair Cells

The receptor end organs in each ear of the vestibular system include the three cristae ampullares (one crista located in the ampulla of each semicircular duct) and the maculae of the utricle and saccule (*see* **Fig. 16.7**). The three semicircular ducts, oriented at right angles to each other, represent the three dimensions of space. The membranous labyrinths of the semicircular canals, utricle and saccule, are filled with endolymph (continuous with the cochlear duct) and surrounded by perilymph in the osseous labyrinth (continuous with the scala vestibuli and scala tympani of the cochlea).

The many stereocilia and single kinocilium of a hair cell in each crista are embedded in a gelatinous matrix (*cupula*) that abuts against the roof of the ampulla; the *kinocilium* of each hair cell is located on one side of all stereocilia (*see* **Fig. 16.8**). The kinocilium is a true cilium and the stereocilia, as in the organ of Corti, are microvilli. Each vestibular hair cell is depolarized when the stereocilia bend in the direction of the kinocilium and is hyperpolarized when deflected in the opposite direction; evidence indicates that the axis of sensitivity is retained

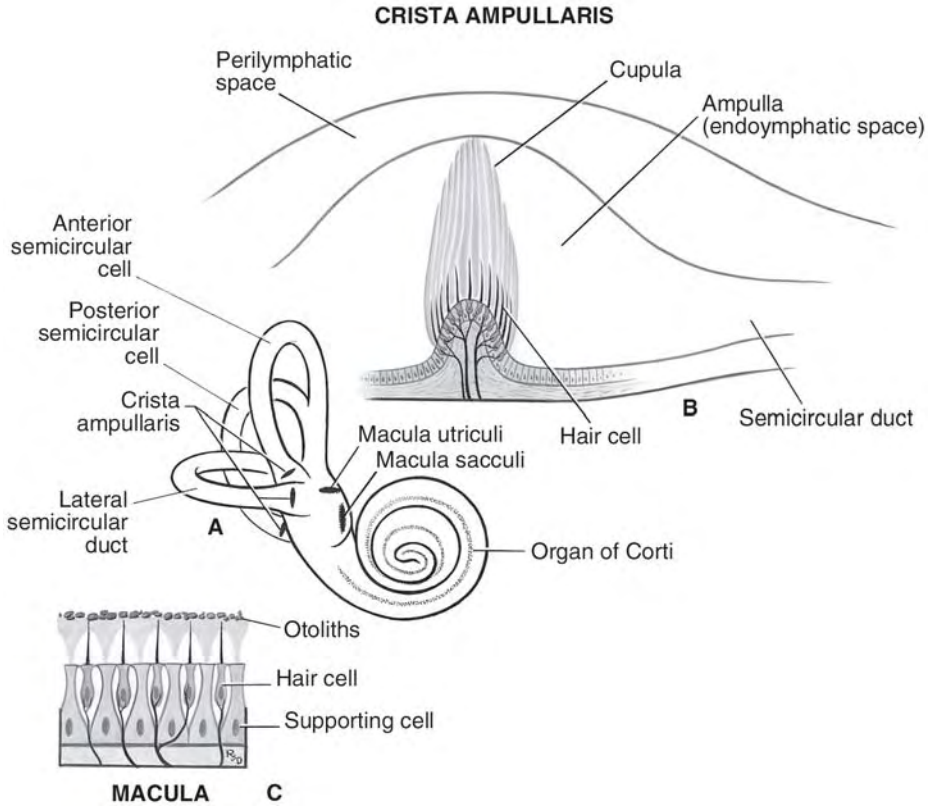


Figure 16.7: (A) The right membranous labyrinth as viewed from the front. Neuroepithelial areas (in black) include a crista ampullaris in the ampulla of each semicircular duct, the macula of the utricle, the macula of the saccule, and the spiral organ of Corti of the cochlear duct. **(B)** The crista ampullaris in a semicircular duct. Stereocilia are embedded in the gelatinous cupula, which extends to the wall of the ampulla. **(C)** The macula. Stereocilia and the kinocilium of hair cells protrude through the gelatinous cover; their tips contact the otoliths on the surface.

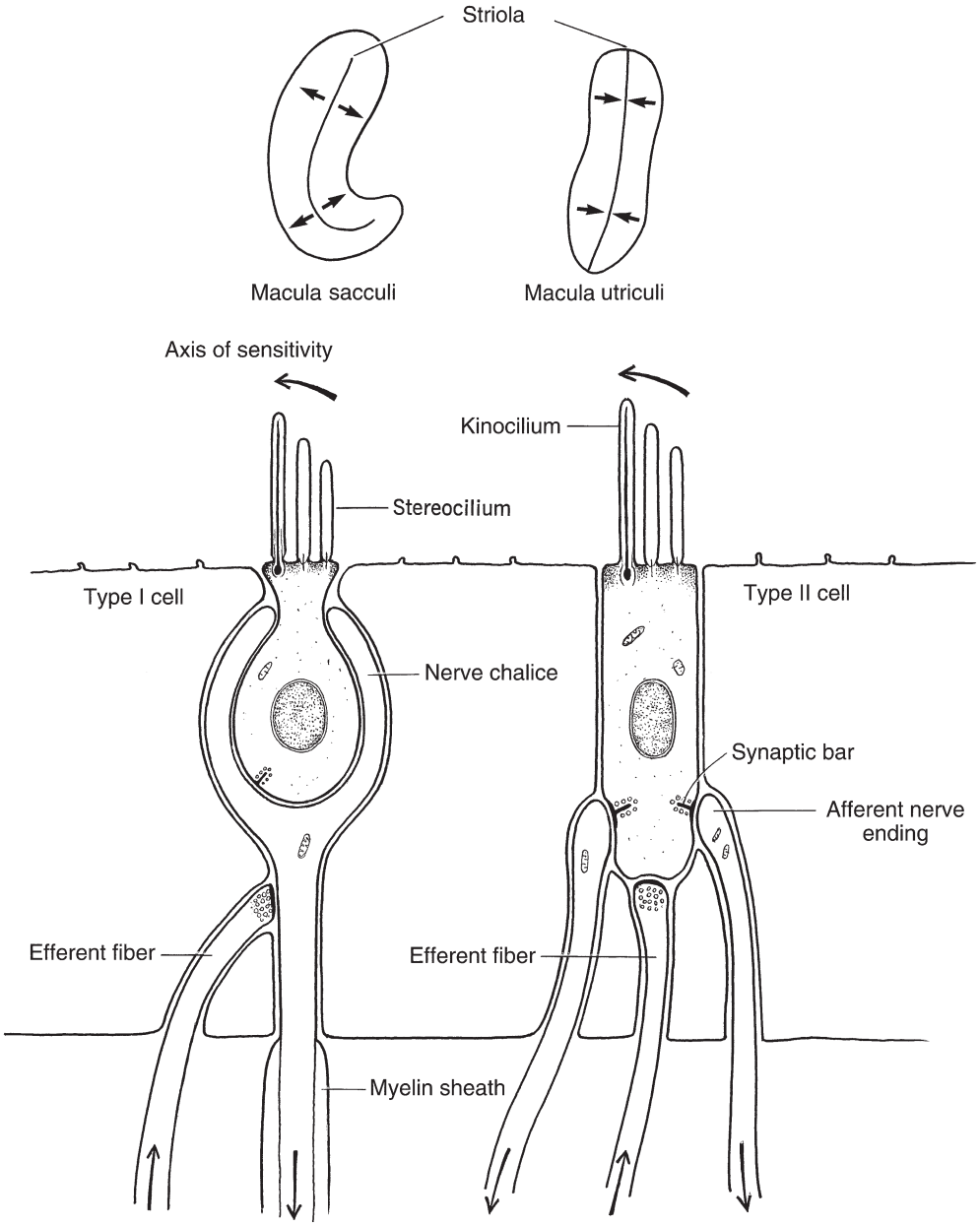


Figure 16.8: Schematic drawing of type I and type II vestibular hair cells in the macula (utricle and saccule) and in the crista ampullaris of each semicircular canal. Vestibular receptors have a true kinocilium; bending of the hair bundle toward the kinocilium elicits depolarization, whereas bending in the opposite direction produces hyperpolarization. The type I cell is enveloped by a primary afferent nerve fiber, and as in the cochlea, efferents from the brainstem form axo-axonal synapses on the afferent fibers. Vestibular efferents terminate directly on type II hair cells. The maculae have a central band called the striola. The axis of sensitivity is toward the striola in the utricle and away from it in the saccule.

in the absence of kinocilia. The mechanisms of transduction are the same as for the auditory receptors. All hair cells in a crista are polarized in the same direction. The cristae ampullares respond to angular movements and only to acceleration and deceleration, not constant movement of the head. Thus, these receptors act as angular accelerometers that respond to the twists and turns of the head.

The movement of endolymph within the semicircular ducts as the head turns and rotates results in the bending of the cupula and cilia. Semicircular ducts of the two sides operate in pairs: the two horizontal ducts are yoked, as are the anterior duct of one side with the posterior duct of the opposite side. The kinocilia of the horizontal ducts, in contrast to those of the other ducts, face the utricle (i.e., toward the midline). Thus, rotation to the left causes (1) deflection of the stereocilia in the left horizontal duct toward the kinocilium and in the right duct away from the kinocilium, (2) depolarization of hair cells in the crista ampullaris of the left horizontal duct and hyperpolarization in the right crista, and (3) increased frequency of impulses in the left vestibular nerve leading from the horizontal duct and decreased frequency in the right nerve. The vestibular nerve has a spontaneous firing rate of about 100 impulses per second.

The macula of the saccule is oriented with its long axis essentially in a vertical plane, and the macula of the utricle in a horizontal plane. The stereocilia and kinocilium of each hair cell, similar to those in the crista ampullares, are embedded in a gelatinous matrix (*see* **Fig. 16.7**). However, in the maculae, there is a layer of calcareous crystals (*otoliths*) that amplify the force caused by deflection of the stereocilia. Additionally, the stereocilia are polarized in relation to a curved band, the *striola*, which passes through the central portion of the maculae. In the utricle, all kinocilia face the striola, whereas in the saccule, they face in the opposite direction (away from the striola). Thus, unlike the crista ampullares, individual receptors contain some hair cells that are depolarized at the same time others are hyperpolarized. The two maculae, also called otolith organs, are really linear accelerometers. The saccular macula responds to vertically directed acceleratory and deceleratory linear displacements and gravity (e.g., movements up and down in an elevator). The utricular macula responds to horizontally directed forces and gravity.

The role of the vestibular receptors in the orientation of the head and body in space is expressed through muscle actions that coordinate eye reflexes, head position and body movements. These specialized proprioceptors tend to (1) reinforce the tonic activity of muscles while in a stationary position (e.g., maintain balance while standing in a moving vehicle) and (2) trigger muscle reflexes in response to changes in position of the head, body, and extremities (e.g., sustain balance while walking a tightrope).

Input to the Vestibular Nuclei (*see* Figs. 16.9 and 18.5)

The sensory neurons of the vestibular nerve (cell bodies in the vestibular ganglion) are bipolar with distal branches that terminate on the hair cells of the vestibular receptors (maculae and cristae ampullares). Most of the centrally directed axons terminate ipsilaterally within the brainstem in precise synaptic patterns within each of the four vestibular nuclei (superior, lateral, medial, and inferior). In general, the fibers originating from the cristae ampullares end in the medial and superior nuclei; the fibers originating in the maculae of the utricle and saccule terminate primarily in the lateral, inferior, and medial vestibular nuclei. Other fibers of the vestibular nerve course through the juxtarestiform body (medial part of the inferior cerebellar peduncle; *see* **Fig. 18.5**) and end directly in the ipsilateral cerebellar cortex, chiefly in the flocculonodular lobe, which is referred to as the vestibulocerebellum. In addition, this cortex and the fastigial nuclei of the cerebellum send crossed and uncrossed fibers to the vestibular nuclei. In summary, the vestibular nuclei receive their main input both from the vestibular receptors and the cerebellum. In addition, the vestibular nuclei have

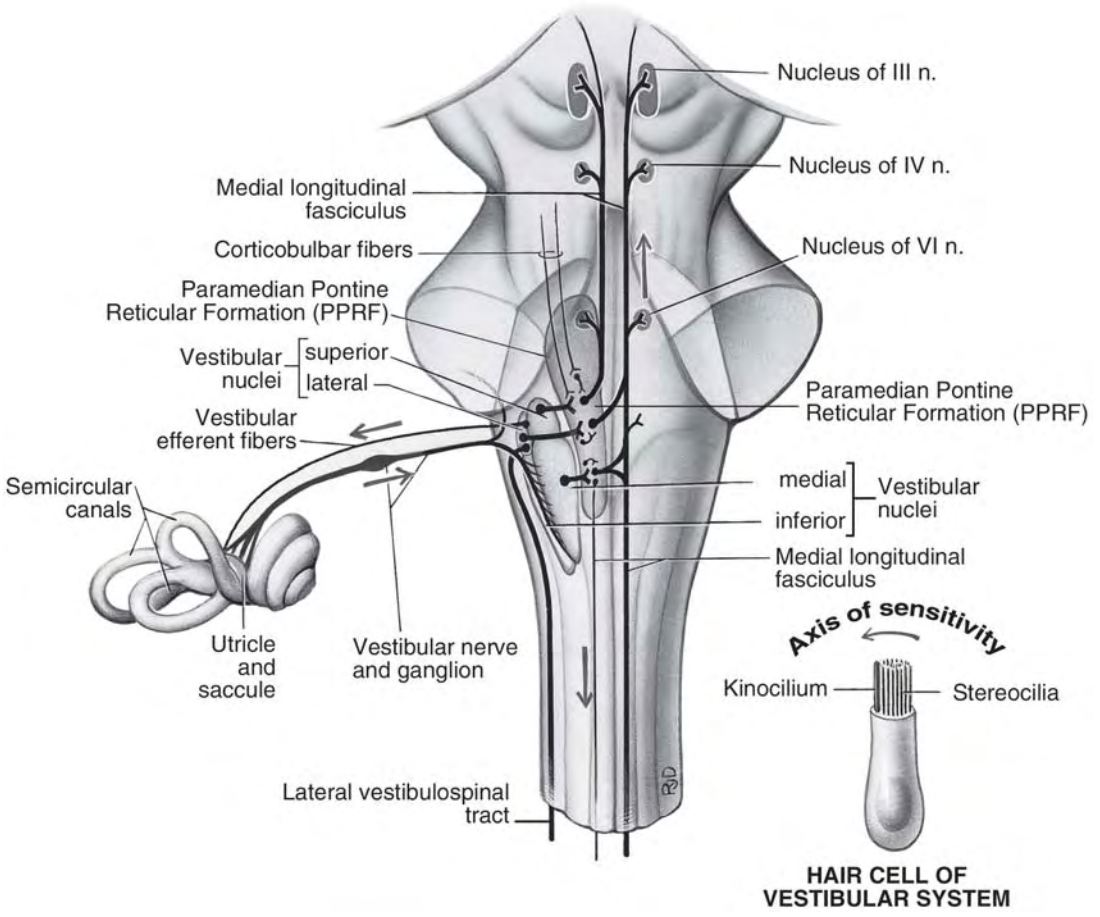


Figure 16.9: Principal vestibular pathways in the brainstem and spinal cord. Interconnections between the vestibular system and the vestibulocerebellum are illustrated in Fig. 18.5. The inset shows a vestibular hair cell whose axis of sensitivity is in the direction of the kinocilium.

reciprocal connections with the flocculonodular lobe and nuclei fastigii of the cerebellum.

Output From the Vestibular Nuclei

The influences from the vestibular nuclei are projected (1) to the spinal cord via the (lateral) vestibulospinal tract and medial vestibulospinal tract (within medial longitudinal fasciculus [MLF]) (*see* **Fig. 16.9**), (2) to the cerebellum via fibers in the juxtarestiform body (*see* **Fig. 18.5**), (3) to the brainstem primarily via the MLF (vestibulomesencephalic fibers), and (4) to the postcentral gyrus between areas 2 and 5 (see Chap. 23) via a relay in the ventral posterior inferior thalamic nucleus.

Postural Pathways

The *(lateral) vestibulospinal tract*, originating from the lateral vestibular nucleus, is an uncrossed, somatotopically organized bundle of fibers terminating all levels of the spinal cord mainly in laminae VII and VIII (*see* **Figs. 7.5 and 16.9**). It conveys excitatory influences for extensor muscle tone and extensor reflexes. The much smaller *medial vestibulospinal tract*, originating from the medial vestibular nucleus,

is primarily an uncrossed fascicle that descends in the MLF and terminates mainly at cervical levels. It participates in coordination of head position in equilibratory responses and with eye movements to maintain fixation. These descending vestibular tracts act mainly through spinal interneurons on both alpha and gamma motoneurons that go to axial and proximal limb muscles. Their influence in concert with local myotatic reflexes is to maintain the tonus of the extensor muscles of the trunk (back musculature) and the limbs. These neural activities are critical for the support of the body against gravity (i.e., for the maintenance of upright posture).

Vestibuloocular Pathways

One of the most important tasks of the vestibular system is its role in influencing the conjugate (i.e., coupled) movements of the eyes. These conjugate movements are controlled by inputs from many sources (e.g., from areas 8, 18, and 19 of the cerebral cortex) and by means of inputs to the vestibular system. The paramedian pontine reticular formation (PPRF; also called *pontine gaze center*), located medially in the reticular formation, and its rostral continuation in the midbrain is a critical staging region in the central control of eye movements. It acts as a nuclear processing complex and contains a variety of cell types whose activity determines the form of many eye movements. Input to neuronal pools within the PPRF is derived from the cerebral cortex, superior colliculus, cerebellum, auditory and vestibular systems, and the spinal cord. Output from the PPRF is conveyed by circuits utilizing the MLF and the reticular formation and terminating in the motor nuclei of cranial nerves III, IV, and VI, which innervate the extraocular muscles. The vestibulomesencephalic circuit for conjugate eye movements comprises the vestibular nuclei to PPRF to the nucleus of n. VI (in lower pons) and via MLF to the nuclei of n.III and n.IV (in the midbrain). The abducens and oculomotor nuclei also are reciprocally interconnected directly via fibers that travel in the MLF and by way of linkages through the MLF with the PPRF (*see* **Fig. 16.10**). Through these, the PPRF is associated with lateral gaze movements and horizontal saccades.

Vestibular influences are conveyed cephalically via relays in the ventral posterior inferior thalamic nucleus (part of the ventral posterior nucleus) that project to the postcentral gyrus, as noted previously. This pathway is involved in perception of subjective sensations (e.g., dizziness) associated with the vestibular system.

Vestibular Tests and Disorders

Nystagmus. Nystagmus refers to involuntary rhythmic movements of the eyes with a rapid movement in one direction (called a saccade) followed by a slow movement in the opposite direction. It is related to an imbalance of synchronized impulses from vestibular sources. Nystagmus can be elicited and used in tests of vestibular function; when it occurs spontaneously, it can be a symptom of a lesion.

Nystagmus in the normal individual has the following basis. As the head and body pivot and circle, the eyes attempt to fixate on an object in space (slow component); as the head and body continue to circle, the eyes snap quickly in the direction in which the head is circling (fast or quick component). The action is similar to what happens when watching telegraph poles from a moving train (the fast component is in the direction in which the train is moving). These eye movements repeat throughout the duration of the circling. By convention, nystagmus is named by the direction of the fast saccade component. Horizontal nystagmus is the commonest form. Vertical and rotatory nystagmus occur less frequently.

Nystagmus can occur following irritative or destructive lesions of a vestibular end organ, vestibular nerve, vestibular pathways, brainstem or cerebellum. Certain toxic substances can also cause nystagmus.

Sudden recurrent attacks of *vertigo* and nystagmus occur in *Meniere's disease*. This is usually accompanied by tinnitus, unilateral deafness, and varying degrees of nausea and vomiting. The condition is thought to be a consequence of increased pressure and dilatation

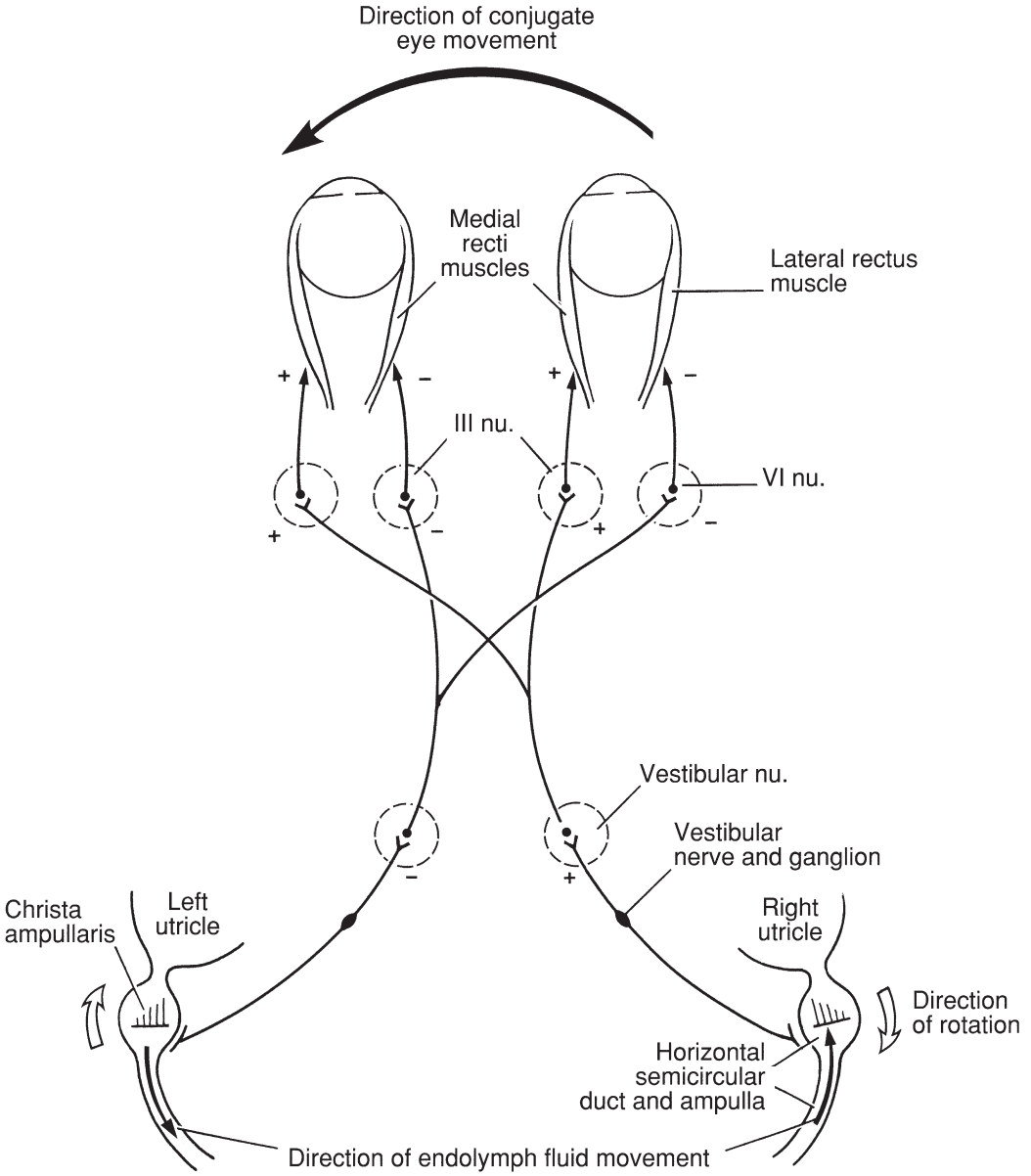


Figure 16.10: Conjugate eye movements associated with the horizontal semicircular ducts and ampullae. Rotational acceleration of the head in a clockwise direction to the right (outlined arrows outside the ampullares) results in a relative movement of endolymph in the paired semicircular ducts to the left (solid arrows in the ducts). Movement of the endolymph toward the utricle results in excitatory activity (+) in the hair cells of the right ampulla and away from the utricle results in inhibitory activity (–) in the hair cells in the left ampulla. These activities result in excitation (+) and inhibition (–) in the medial and superior vestibular nuclei and fibers of the MLF; this produces excitatory and inhibitory influences in appropriate motoneurons in the abducens (lateral rectus muscles) and oculomotor (medial rectus muscles) nuclei to elicit conjugate eye movement to the left (solid arrow).

of the membranous labyrinth resulting from edema.

Rotation Test. The paired horizontal semicircular canals can be tested by placing the subject in a rotating (Bárány) chair and tilting the head forward by 30° to bring the horizontal canals parallel to the ground. The chair is quickly rotated 10–12 turns before being abruptly stopped. The endolymph continues to "flow" in the same direction, deflecting the crista ampullaris of each horizontal canal. A whirling sensation follows. The impulses from the vestibular source stimulate the eye movements, and the visual impulses from the eyes, in turn, create the conscious spinning sensation (*vertigo*). During the spin of the chair to the right, the fast component (saccade) in the normal individual is to the right. Immediately after the spin is stopped, each saccade (postrotatory nystagmus) is reversed and is now directed to the left (called nystagmus to the left). By placing the head in appropriate planes, the other pairs of semicircular canals can be tested. The right anterior and the left posterior semicircular canals are paired, as are the right posterior and the left anterior semicircular canals.

Caloric or Thermal Test. The semicircular canals can be tested calorically by irrigating the external auditory meatus with warm (or cold) water. This elicits convection currents in the endolymph, deflecting the crista ampullaris. Each side of the vestibular apparatus can be tested separately. For example, each horizontal semicircular canal is examined by having the patient sit with the head tilted backward about 60°, bringing the horizontal semicircular canal to the vertical plane. Normally, the nystagmus is to the tested side after warm water is used (and to the opposite side after cold water is used).

Motion Sickness. Dizziness, feeling of lightheadedness, headache, nausea, and vomiting are symptoms associated with motion sickness (seasickness and airsickness). Motion sickness, whether on the sea, in the air, or on the ground (highway), is apparently the response to an excess of accelerations and decelerations as monitored by the vestibular receptors and projected to the brain. Deaf mutes, who lack receptors in the membranous labyrinths, do not experience motion sickness. Drugs such as Dramamine raise the threshold of vestibular stimulation and, thereby, ameliorate the symptoms of motion sickness. Four out of every 10 astronauts experience motion sickness during space missions. This affliction is thought to be related to a discordance of signals monitored by the eyes, proprioceptors in the body, and the vestibular receptors in the head and projected to the brain during the novel conditions of weightlessness.

Central influences are conveyed via vestibular efferent fibers from the brainstem, which pass through the vestibular nerve and terminate on the hair cells of the vestibular end organs. Vestibular efferent fibers probably exert inhibitory effects, which ameliorate influences that might result in motion sickness and nystagmus.

In a general way, the vestibular system helps us appreciate a sense of motion and assists in keeping our balance. Perhaps its finest expression is in such maneuvers as gymnastics, but even when running up a spiral staircase the vestibular system is fully engaged in its remarkable coordination of the movements of the eyes, head, trunk, and extremities.

SUGGESTED READINGS

Fernandez C, Lysakowski A, Goldberg JM. Hair-cell counts and afferent innervation patterns in the cristae ampullares of the squirrel monkey with a comparison to the chinchilla. *J. Neurophysiol.* 1995;73:1253–1269.

Goldberg JM. Afferent diversity and the organization of central vestibular pathways. *Exp. Brain Res.* 2000;130:277–297.

Goldberg JM, Brichta AM. Evolutionary trends in the organization of the vertebrate crista ampullaris. *Otolaryngol. Head Neck Surg.* 1998;119: 165–171.

Griffiths TD. Central auditory pathologies. *Br. Med. Bull.* 2002;63:107–120.

Griffiths TD, Bates D, Rees A, Witton C, Gholkar A, Green GG. Sound movement detection deficit due to a brainstem lesion. *J. Neurol. Neurosurg. Psychiatry* 1997;62:522–526.

Griffiths TD, Green GG, Rees A, Rees G. Human brain areas involved in the analysis of auditory movement. *Hum. Brain Mapping* 2000;9:72–80.

Highstein SM, Fay RR, Popper AN, eds. *The Vestibular System.* New York: Springer-Verlag; 2004.

Hudspeth AJ. How the ear's works work: mechanoelectrical transduction and amplification by hair cells of the internal ear. *Harvey Lect.* 2001;97: 41–54.

Hudspeth AJ, Logothetis NK. Sensory systems. *Curr. Opin. Neurobiol.* 2000;10:631–641.

Jones EG. Chemically defined parallel pathways in the monkey auditory system. *Ann. NY Acad. Sci.* 2003;999:218–233.

Minor LB, Goldberg JM. Vestibular-nerve inputs to the vestibulo-ocular reflex: a functional-ablation study in the squirrel monkey. *J. Neurosci.* 1991; 11:1636–1648.

Moore JK. Organization of the human superior olivary complex. *Microsc. Res. Tech.* 2000;51:403–412.

Moore JK. Maturation of human auditory cortex: implications for speech perception. *Ann. Otol. Rhinol. Laryngol.* 2002;189(Suppl.):7–10.

Poremba A, Saunders RC, Crane AM, Cook M, Sokoloff L, Mishkin M. Functional mapping of the primate auditory system. *Science* 2003;299: 568–572.

Warren JD, Zielinski BA, Green GG, Rauschecker JP, Griffiths TD. Perception of sound-source motion by the human brain. *Neuron* 2002;34: 139–148.

Rivera-Dominguez M, Agate FJ Jr, Noback CR. Scanning electron microscope observation of the organ of Corti of the rhesus monkey. *Brain Res.* 1974;65:159–164.

Wong D, Pisoni DB, Learn J, Gandour JT, Miyamoto RT, Hutchins GD. PET imaging of differential cortical activation by monaural speech and nonspeech stimuli. *Hear. Res.* 2002; 166:9–23.

Zhang LI, Tan AY, Schreiner CE, Merzenich MM. Topography and synaptic shaping of direction selectivity in primary auditory cortex. *Nature* 2003;424:201–205.

17
Lesions of the Brainstem

General Statement
Blood Supply of the Brainstem
Medial Zone of the Medulla
Posterolateral Medulla
Region of the Cerebellopontine Angle (CPA Syndrome)
Medial and Basal Portion of the Caudal Pons
Medial Longitudinal Fasciculus
Lateral Half of the Midpons
Basal Region of the Midbrain (Weber's Syndrome)
Upper Midbrain Tegmentum (Benedikt's Syndrome)
Lesions of Both Superior Colliculi (Parinaud's Syndrome)

The effects of a lesion depend on the anatomic and physiologic roles of the neurons and tracts damaged. In general, tracts passing through or commencing within the brainstem are oriented in a plane parallel to the long axis of the brainstem; long tract signs alone are of limited value in determining the level of injury. Examples are the spinothalamic tract, medial lemniscus, and pyramidal tract. Cranial nerves, however, course in a plane perpendicular to the long axis. For this reason, they are helpful in localizing the level of a lesion, and together with long tract signs, the precise site of a lesion can be determined. Thus, these orientations, longitudinal and transverse, should be kept in mind in the following account (*see* **Figs. 13.7 to 13.16, 14.2, and 14.3**).

GENERAL STATEMENT

The long ascending (sensory) and descending (motor) pathways are generally involved with sensory and motor expressions of the opposite side of the body. Ten pairs of cranial nerves emerge from the brainstem: midbrain, III and IV; pons, V; pons–medulla junction, VI, VII, VIII; medulla, IX, X, XI, XII; and one from the cervical spinal cord, spinal XI. They express their roles on the same side of the body, with the exception of the ipsilateral trochlear nerve, which decussates within the substance of the midbrain. Thus, depending on location, a unilateral lesion can result in signs on the opposite side of the body (lesion of a pathway) and the same side of the head (lesion of one or more cranial nerves).

Depending on the level, a *unilateral lesion of the brainstem* can result in (1) contralateral loss of position and vibratory sense (medial lemniscus in medulla or pons), (2) contralateral hemiplegia (corticospinal tract in medulla, pons, or midbrain), and (3) ipsilateral lower-motoneuron paralysis of the tongue (cranial nerve XII, medulla), lateral rectus (VI, pons–medulla junction), and the other extraocular muscles, not including the superior oblique, together with the elevator of the eyelid (III, midbrain).

A *unilateral lesion in the lateral medulla* can result in (1) contralateral loss of pain and temperature from the body (lateral spinothala-

mic tract), (2) ipsilateral loss of pain and temperature from the face (spinal tract and nucleus of n.V), (3) ipsilateral Horner's syndrome (*see* later, descending sympathetic fibers), (4) nystagmus (vestibular nuclei; Chap. 16), and (5) unsteady ipsilateral extremities (input to cerebellum; Chap. 18). The combination of the loss of pain and temperature on the ipsilateral side of the head and the contralateral side of the body is called *alternating hemianesthesia*.

Lesions of the following pathways within the brainstem result in signs on the opposite side of the body and occiput because the tracts are crossed: spinothalamic (decussates in spinal cord), medial lemniscus (decussates in lower medulla), and corticospinal (decussates in lower medulla). In their course through the brainstem, (1) the spinothalamic tract is located in the lateral tegmentum, (2) the medial lemniscus shifts as it ascends from a position in the anteromedial tegmentum in the medulla to the posterolateral tegmentum in the midbrain before terminating in the ventral posterior lateral thalamic nucleus, and (3) the corticospinal tract descends through the medial portion of the brainstem.

A unilateral lesion of the auditory pathway above the level of the cochlear nuclei results in only subtle changes in most auditory perceptions because of the strongly bilateral nature of the auditory pathway. The ability to localize sound direction is diminished. The thresholds for sound intensity are unaffected. Unilateral lesions destroying the cochlear nuclei produce deafness on the ipsilateral side because auditory fibers are interrupted prior to their decussation. Deafness in one ear more commonly is caused because of inner-ear disease.

A unilateral lesion of the anterior trigeminothalamic tract in the pons and midbrain is accompanied by loss of pain and temperature on the forehead, face, nasal cavity, and oral cavity on the opposite side. This occurs because the lesion is *above* the level where the fibers of this tract decussate in the medulla.

Cranial nerves III (midbrain), VI (pons–medulla junction), and XII (medulla) emerge on the anterior aspect of the brainstem in close proximity to the descending corticospinal tract. Injury to one of these nerves and the corticospinal tract results in an *alternating hemiplegia*—the lesion to the nerve produces a lower-motoneuron (LMN) paralysis on the *same side* of the head, and the lesion to the corticospinal tract produces an upper-motoneuron (UMN) paralysis on the *opposite side* of the body (because the lesion is rostral to the level of the tract's decussation). A partial paralysis of voluntary muscles innervated by lower motoneurons is known as a *paresis* or *palsy* and that of muscles supplied by motoneurons of the bulb (medulla) is known as a *bulbar palsy*. Usually, unless damage to corticobulbar fibers is bilateral, unilateral lesions lead to little, if any, motor disturbances, with the exception of the lower facial muscles. The motor and premotor cortices emit substantial bilateral projections to the lower motor neurons of the muscles of facial expression above the level of the eyes. In contrast, cortical projections to LMNs that innervate the muscles of facial expression below the eyes are mainly crossed with only a modest uncrossed component. Thus, a unilateral lesion of the corticobulbar fibers causes an UMN paralysis on the contralateral side limited to the muscles of facial expression below the level of the eye (*see* Chap. 11, corticobulbar tract). When the corticobulbar tracts (upper motor neurons) are bilaterally interrupted (e.g., as can occur in multiple sclerosis), the resulting muscle paralysis is known as a *pseudobulbar palsy*. Signs associated with pseudobulbar palsies include dysphagia (difficulty in swallowing), dysarthria (difficulty in articulating speech), and hyperreflexia of the jaw jerk reflex (evoked by tapping the chin gently with the jaw slightly opened).

The branchiomeric nerves (V, VII, IX, X, and XI) pass close to the spinothalamic tract before emerging on the lateral side of the brainstem. Injury to one of these nerves, the spinothalamic tract, and the spinal tract and nucleus of nerve V results in (1) ipsilateral sensory loss from the face and a LMN paralysis of the muscles, innervated by that nerve and (2) loss of pain and temperature on the opposite

side of the body and back of the head because of the interruption of the decussated fibers of the spinothalamic tract.

BLOOD SUPPLY OF THE BRAINSTEM

The sequence of vertebral arteries, basilar artery, and posterior cerebral arteries forms the main trunk system supplying arterial blood to the medulla, pons, midbrain, cerebellum, and posterior medial cerebrum (*see* **Figs. 4.1 and 4.2**). The paired vertebral arteries ascend along the anterolateral aspect of the medulla and join at the pons–medulla junction to form the single midline basilar artery, which ascends and then divides in the midbrain region into the paired posterior cerebral arteries. Branches of these arteries supply the brainstem in patterns that can be generalized as follows: paramedian branches are distributed to a medial zone on either side of the midsagittal plane, short circumferential branches are generalized to an anterolateral zone, and long circumferential branches are generalized to a posterolateral zone and to the cerebellum (*see* **Fig. 17.1**).

MEDIAL ZONE OF THE MEDULLA

The occlusion of an anterior spinal artery and its paramedian branches to the medial zone of the medulla can cause a lesion that involves the hypoglossal nerve (n.XII), corticospinal tract in the pyramid, and medial lemniscus (*see* **Fig. 17.2A**). The resulting *alternating hemiplegia* combines a lower-motoneuron (LMN) paralysis of the tongue on the ipsilateral side (n.XII) with an upper-motoneuron (UMN) paralysis and a loss of discriminatory general senses (medial lemniscus) on the contralateral side of the body and both limbs. Recall that the corticospinal tract decussates at the junction of the medulla and cervical spinal cord and that the posterior column–medial lemniscus pathway decussates in the lower medulla. During the first few weeks after the lesion, the ipsilateral half of the tongue fibrillates because of denervation sensitivity; later, the muscles atrophy and that side of the tongue appears wrinkled. When protruded, the tongue deviates to the paralyzed side due primarily because of the unopposed action of the contralateral genioglossus muscle. The contralateral side of the body exhibits signs of an UMN paralysis (corticospinal tract) and loss of position, muscle and joint sense, impaired tactile discrimination, and loss of vibratory sense (medial lemniscus), because the lesion interrupts these tracts above the level of their decussation.

Immediately after the vascular occlusion, the upper and lower limbs on the contralateral side exhibit a hypotonus with weakness, decreased stretch reflexes (deep tendon reflexes), diminished resistance to passive manipulation, loss of superficial reflexes, and loss of response to plantar stimulation of the foot. This is known as *spinal shock.* After a month or so following the stroke, the contralateral limbs develop a spastic paralysis, hypertonia with weakness, clasp-knife resistance to passive movement, hyperreflexia, loss of superficial reflexes, and the Babinski (extensor plantar) reflex.

POSTEROLATERAL MEDULLA

Failure of the posterior inferior cerebellar artery (PICA), a long circumferential artery, can cause a lesion resulting in the *lateral medullary syndrome (Wallenberg's syndrome)* (*see* **Fig. 17.2B**). Damage to the following structures produces the symptoms: spinothalamic tract; spinal trigeminal tract and nucleus; fibers and possibly nuclei associated with the glossopharyngeal nerve, vagus nerve, spinal portion of the accessory nerve (including the nucleus ambiguus, dorsal vagal nucleus, tractus, and nucleus solitarius), and portions of the reticular formation, vestibular nuclei, and the inferior cerebellar peduncle. Symptoms include the following:

1. Loss of pain (*analgesia*) and temperature sensation (*thermoanesthesia*) on the opposite side of the body, including the back of the head (crossed spinothalamic tract).

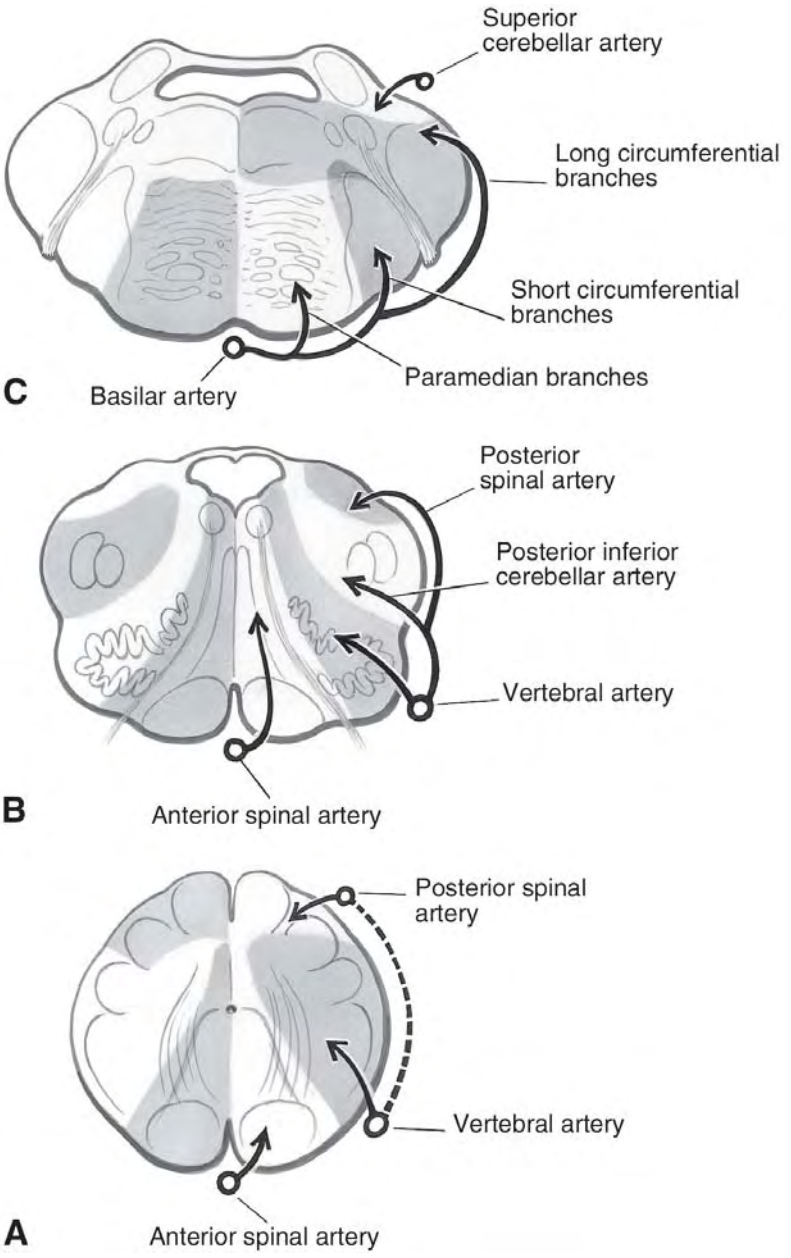


Figure 17.1: The patterns of arterial supply of the branches of the vertebral–basilar system within the **(A)** caudal medulla, **(B)** midmedulla, and **(C)** pons. (Refer to Fig. 4.1.)

2. Loss of pain and temperature on the same side of the face and nasal and oral cavities in all three trigeminal divisions (uncrossed spinal trigeminal tract and nucleus). The combination of symptoms 1 and 2 is an *alternating hemianesthesia*.
3. Difficulty in swallowing and a voice that is hoarse and weak. This is caused by damage

to the nucleus ambiguus. A lesion of the nucleus ambiguus on one side results in an ipsilateral paralysis of the palatal, pharyngeal, and laryngeal muscles, all innervated by cranial nerves IX, X, and the cranial division of XI. Difficulty in the initial stage of swallowing is the result of paralysis of some palatal muscles and adjacent regions. Difficulty in later stages of swallowing (dysphagia) is the result of paralysis of the pharyngeal muscles. The palate and uvula deviate to the nonparalyzed side during vocalization. The hoarseness occurs because of paralysis of the musculature controlling the ipsilateral vocal cord.

4. Loss of gag reflex on the ipsilateral side and absence of sensation on the ipsilateral side of the fauces (glossopharyngeal nerve).
5. Disturbances in equilibrium because of damage to part of the inferior cerebellar peduncle.
6. Nausea and vertigo because of damage to the vestibular nuclei and vestibulocerebellum.

A bulbar palsy occurs following degeneration of motoneurons of the medulla. A transient tachycardia (increase in heartbeat) can result from sudden withdrawal of some parasympathetic innervation; compensatory mechanisms, including influences from the contralateral vagus nerve, restore normal heartbeat. The absence of afferent stimulation from some visceral receptors (e.g., carotid body and carotid sinus) to the solitary nucleus is compensated for by the input from similar receptors on the unaffected contralateral side. The interruption of spinocerebellar and other fibers passing through the inferior cerebellar peduncle results in signs of cerebellar malfunction on the ipsilateral side of the body, including hypotonia, ataxia, and poorly coordinated voluntary movements (Chap. 18). Irritation of the vestibular nuclei can cause nystagmus and/or deviation of the eyes to the ipsilateral side. Horner's syndrome (constricted pupil, ptosis of eyelid, and absence of sweating from half of the face) on the same side can occur if many descending fibers of the autonomic nervous system and reticulospinal tracts to the thoracic sympathetic outflow are disrupted. Tactile and discriminative general senses from the face are normal because the principal sensory nucleus of n.V and its ascending pathways are above the level of the lesion.

REGION OF THE CEREBELLOPONTINE ANGLE (CPA SYNDROME)

Acoustic neuromas are slow-growing tumors that originate from neurolemmal

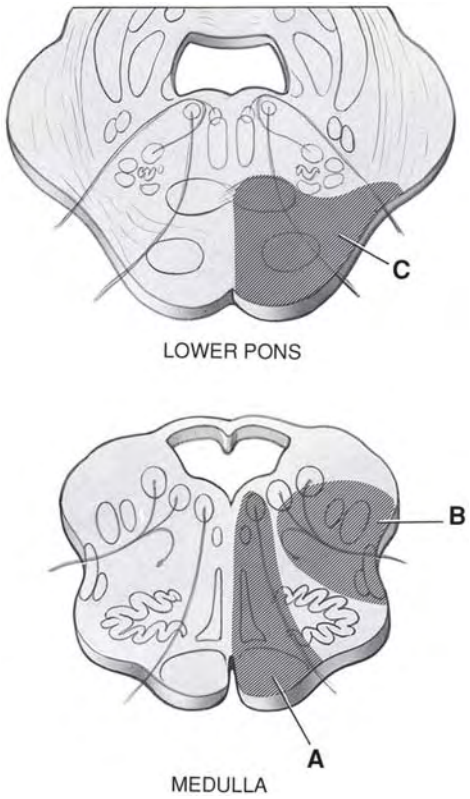


Figure 17.2: Sites of lesions in the lower brainstem as described in the text. In the medulla, the lesions are located **(A)** in the medial zone and **(B)** in the posterolateral tegmentum. In the lower pons, the lesions are located **(C)** in the anteromedial tegmentum and basilar portion.

(Schwann) cells of the vestibular nerve. Those in the vicinity of the internal auditory foramen can extend into the *cerebellopontine angle (CPA)*, the junction of the cerebellum, pons, and medulla near the emergence of cranial nerves VII and VIII (*see* **Fig. 14.1**). In the early stages, symptoms are referable to the eighth cranial nerve; they include (1) tinnitus (ringing in the affected ear) followed by progressive deafness on the lesion side and (2) abnormal labyrinthine (vestibular) responses, such as tilting and rotation of the head with the chin pointing to the lesion side and, at times, horizontal nystagmus. As the tumor enlarges, it exerts pressure on the brainstem and damages the inferior and middle cerebellar peduncles, spinothalamic tract, spinal trigeminal tract and facial nerve. The cerebellar signs that result from the involvement of the cerebellar peduncles include coarse intention tremor, dysmetria, an ataxic gait, dysdiadochokinesis, and hypotonia on the lesion side (Chap. 18). The loss of pain and temperature sensation on the ipsilateral side of the face, oral and nasal cavities, and on the contralateral side of the body are a consequence of damage to the spinal trigeminal tract and spinothalamic tract, respectively; this combination of ipsilateral and contralateral sensory loss is called *alternating hemianesthesia*. Injury to the facial nerve results in an ipsilateral LMN paralysis of the muscles of facial expression, loss of the corneal reflex on the injured side, and hyperacusis (*see* Chap. 14, "Lesion of the Facial Nerve"). Due to interruption of the intermediate root of n. VII, there is an ipsilateral loss of taste on the anterior two-thirds of the tongue; lacrimation and salivation also are affected.

MEDIAL AND BASAL PORTION OF THE CAUDAL PONS

The occlusion of paramedian and short circumferential branches of the basilar artery can result in damage to the following structures within the confines of the lesion: abducent nerve (n.VI), facial nerve (n.VII), pyramidal tract, and medial lemniscus (*see* **Fig. 17.2C**).

The interruption of the fibers of n.VI (lower motoneurons) and the pyramidal tract (upper motoneurons) results in an alternating abducent hemiplegia. The transection of n.VI on one side produces a medial deviation (adduction) of the affected eye from the unopposed pull of the medial rectus muscle (eye is cocked in). There is also horizontal diplopia (double vision) because the image of an object falls on noncorresponding portions of the two retinas and is seen as two objects. Diplopia is maximal when the patient attempts to gaze to the lesion side. It is minimal (or absent) when gaze is directed to the side opposite the lesion because the unaffected eye and the affected eye are viewing the same visual fields. As already stated, damage to the corticospinal tract causes a contralateral hemiplegia and injury to the medial lemniscus causes a loss of discriminatory general senses (*see* "Medial Zone of the Medulla"). Interruption of n. VII causes an ipsilateral LMN facial paralysis, hyperacusis, and disturbances in taste perception, lacrimation, and salivation.

MEDIAL LONGITUDINAL FASCICULUS

Lesions of the medial longitudinal fasciculus (MLF) just rostral to the abducent nuclei cause *internuclear ophthalmoplegia*, a disturbance of conjugate horizontal eye movements. Usually bilateral, this often is the presenting syndrome in patients who have multiple sclerosis; a unilateral form of internuclear ophthalmoplegia results from a vascular accident. Fibers that synchronize the contractions of the lateral rectus of one eye (abductor innervated by n.VI) and the medial rectus muscle of the opposite eye (adductor innervated by n.III) become demyelinated. Such a lesion in the MLF results in (1) weakness of adduction of the eye when attempting lateral gaze to the opposite side, (2) horizontal nystagmus of the other eye, which abducts but cannot hold the abducted position, and (3) no impairment

with convergence of the two eyes. The observation that the eyes fail to adduct on attempted lateral gaze but do so during convergence shows that the lower motoneurons are intact and, therefore, the loss of adduction in this syndrome is the result of an upper-motoneuron type injury (in this case, internuclear, between the abducent and oculomotor nuclei). Nystagmus in the abducting eye is attributed to interruption of fibers that descend in the MLF from the oculomotor nucleus to the abducent level, where they cross to the opposite abducent nucleus.

LATERAL HALF OF THE MIDPONS

The structures within the region of the lesion (*see* **Fig. 17.3**A) include the trigeminal nerve, spinothalamic tract, lateral lemniscus, medial lemniscus, and the middle cerebellar peduncle. Damage to the trigeminal nerve (n.V) results in (1) the absence of all general senses (anesthesia) on the ipsilateral side of the face, forehead, and nasal and oral cavities (including absence of corneal sensation and the corneal reflex) and (2) a LMN paralysis of the muscles of mastication, with the chin deviating to the lesion side when the mouth is opened. Destruction of the medial lemniscus results in a contralateral loss of position, muscle, and joint sense and impaired vibratory sense and tactile discrimination. If the lesion is extensive enough to include the corticospinal tract, the combination of the pyramidal tract and n.V produces an *alternating trigeminal hemiplegia*.

Coma and the "Locked-in" Syndrome

The brainstem reticular formation contains the anatomic substrates for the reticular activating system projecting to the diencephalon and cerebral cortex (Chap. 22). The reticular system is of importance in the mechanisms of arousal, regulation of the sleep–wake cycle, and the state of alertness.

Extensive rapidly occurring bilateral lesions involving the upper pons and midbrain reticular formation are associated with coma, which is a state of sustained unconsciousness and unresponsiveness. It differs from sleep. which under normal circumstances has a circadian rhythm and from which an individual can be completely aroused.

Bilateral lesions of the basal pons, usually the result of an occlusion of the basilar artery, may completely interrupt the corticobulbar and corticospinal tracts on both sides. Such lesions can spare much of the reticular formation and corticobulbar fibers to the oculomotor nuclei, which terminate in the midbrain. These patients can be completely immobile or "locked-in" but not comatose. They are quadriplegic and unable to speak or move the facial muscles or tongue. However, such patients are fully conscious and can communicate by responding with eye movements because the reticular

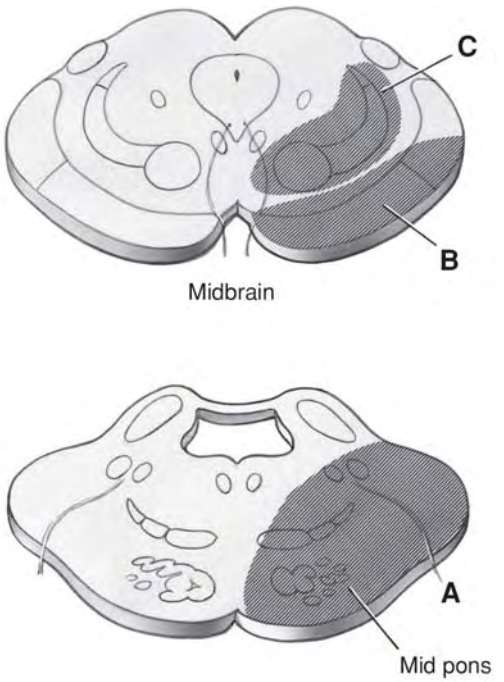


Figure. 17.3: Sites of lesions in the pons and midbrain as described in the text. **(A)** In the midpons, the lesion is located laterally. In the midbrain at the superior colliculus level, the lesions are located **(B)** in the basilar region and **(C)** in the tegmentum.

formation and corticobulbar fibers to the oculomotor nuclei are intact.

BASAL REGION OF THE MIDBRAIN (WEBER'S SYNDROME)

Occlusion of paramedian branches and short circumferential branches of the basilar and posterior cerebral arteries can produce *Weber's syndrome* (*see* **Fig. 17.3B**), which is a consequence of damage to the oculomotor nerve (n.III), the corticospinal tract, and a variable number of corticobulbar and corticoreticular fibers. Interruption of all the fibers in the oculomotor nerve results in signs restricted to the ipsilateral eye, including drooping of the eyelid (*ptosis*, or inability to raise the eyelid because of paralysis of the levator palpebrae muscle); diplopia (double vision), external *strabismus* (squint) because of unopposed contraction of the lateral rectus muscle (the eye remains maximally abducted), inability to elevate, depress, or adduct the eye, and a fully dilated pupil (sympathetic tone is unopposed as a result of the loss of parasympathetic fibers in n.III). The consensual light reflex of the contralateral eye is normal (Chap. 19). An *alternating oculomotor hemiplegia* is a consequence of a LMN paralysis of the extraocular muscles and an UMN paralysis of the contralateral side of the body from damage to the corticospinal tract.

In general, motor nuclei of the cranial nerves (except for the neurons of the facial nucleus innervating the lower face) are supplied by upper motoneurons from both halves of the cerebrum (Chap. 11). Hence, unilateral lesions do not produce an UMN paralysis of the muscles innervated by these nerves, except for weakness of the contralateral muscles of facial expression of the lower face. However, in some cases, interruption of the upper motoneurons to the nucleus ambiguus and hypoglossal nucleus results in contralateral weakness of the muscles of the jaw, soft palate, and tongue; interruption of UMNs to the motor nucleus of n.V (masticatory nucleus) can result in an exaggerated jaw jerk reflex (stretch reflex). The explanation for these occasional observations is that the UMN innervation to the LMN supplying these muscles is similar to the corticobulbar–LMN circuitry to the muscles of facial expression of the lower face; that is, the corticobulbar supply to the part of the facial nucleus innervating the lower face is effectively only crossed. The result is weakness of the muscles of the lower half of the face; the soft palate and uvula will be drawn to the same side as the lesion, and the tongue will deviate to the opposite side when protruded.

Bilateral, diffuse involvement of the corticobulbar and corticoreticular fibers results in a *pseudobulbar palsy*. In this syndrome, there is a bilateral paralysis or weakness without atrophy of many muscles innervated by cranial nerves. The muscle groups affected control chewing, swallowing, speaking, and breathing. Unrestrained crying and laughing occur in many subjects with pseudobulbar palsy. These emotional outbursts can be related to release from cortical and subcortical influences.

UPPER MIDBRAIN TEGMENTUM (BENEDIKT'S SYNDROME)

Benedikt's syndrome results from a unilateral lesion limited to the midbrain tegmentum that includes the fibers of the oculomotor nerve, red nucleus, superior cerebellar peduncle, medial lemniscus, and spinothalamic tract (*see* **Fig. 17.3C**). Damage to the red nucleus and fibers of the superior cerebellar peduncle, which pass through and around it, results in cerebellar signs such as coarse intention tremor, dysdiadochokinesis, cerebellar ataxia, and hypotonia on the contralateral side of the body (Chap. 7). The injury to the third cranial nerve causes a LMN paralysis of the ipsilateral extraocular muscles innervated by the oculomotor nerve and a dilated pupil (mydriasis) because of loss of parasympathetic fibers (*see* Basal Region of the Midbrain). The eye cannot be adducted beyond the midline, elevated or lowered.

Interruption of the crossed spinothalamic tract, trigeminothalamic tract, and medial lemniscus results in the loss of sense of pain, temperature, light touch, vibratory sense, pressure touch, and other discriminatory senses on the opposite side of the body and head. Touch and other discriminatory senses on the contralateral side of the forehead can be retained if the uncrossed posterior trigeminothalamic tract is intact.

LESIONS OF BOTH SUPERIOR COLLICULI (PARINAUD'S SYNDROME)

Tumors of the pineal gland can compress both the superior colliculi and pretectum producing a paralysis of upward gaze. The pupils can be dilated with loss of the light reflex, but they are capable of accommodation.

SELECTED READINGS

Collins RC. *Neurology.* Philadelphia: Saunders; 1997.

Dublin AB, Dublin WB. *Atlas of Neuroanatomy with Radiologic Correlation and Pathologic Illustration.* St Louis, MO: WH Green; 1982.

Gilman S, Winans S. *Manter and Gatz's Essentials of Clinical Neuroanatomy and Neurophysiology.* 10th ed. Philadelphia: FA Davis; 2003.

Patten J. *Neurological Diferential Diagnosis.* New York: Springer-Verlag; 1977.

Rowland LP. *Clinical Syndromes of the Spinal Cord and Brain Stem.* In: Kandel ER, Schwartz JH, Jessell T, eds. *Principles of Neural Science.* 3rd ed. New York: Elsevier; 1991;711–730.

Rowland LP, ed. *Merritt's Neurology.* 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2000.

Victor M, Ropper AH. *Adams and Victor's Principles of Neurology.* 7th ed. New York: McGraw-Hill Medical; 2002.

18 Cerebellum

Gross Anatomy
Subdivisions of the Cerebellum
Salient Features of Function
General Cerebellar Circuitry
Functional Considerations
Cerebellar Dysfunction

The cerebellum is the great coordinator of muscle action and is important for learning motor tasks. It synchronizes contractions of muscles within and among groups, smoothing out responses by delicately regulating and grading muscle tensions. Thus, it plays an important role in equilibrium and muscle tone. Located in the posterior cranial fossa, beneath the tentorium cerebelli and behind the pons and medulla, the cerebellum processes sensory input related to ongoing motor activity, all on an unconscious level. It plays no part in conscious perceptions or in intelligence.

Sensory input to the cerebellum is derived from the vestibular system, stretch receptors (neuromuscular spindles and Golgi tendon organs), and other general sensors in the head and body. The auditory and visual systems also send fibers to the cerebellum. This input is functionally integrated into the motor pathways via outputs mainly to upper motoneurons and cerebellar feedback circuits coming from and going to the cerebral cortex, vestibular system, and brainstem reticular formation.

GROSS ANATOMY

The cerebellum consists of (1) an outer gray mantle, the *cortex*, (2) a *medullary core* of white matter composed of nerve fibers projecting to and from the cerebellum, and (3) four pair of *deep cerebellar nuclei* (*fastigial, globose, emboliform,* and *dentate)*. The globose and emboliform nuclei together constitute the *interposed nucleus*.

The cerebellar surface is corrugated into parallel, long, narrow "gyri" called *folia* (leaves) whose long axes are in the transverse plane; about 15% of the cortex is exposed to the outer surface, whereas 85% faces the sulcal surfaces between the folia. The cerebellum is connected to the brainstem by three pairs of cerebellar peduncles: (1) the *inferior cerebellar peduncle* is a bridge between the medulla and the cerebellum and is composed of fibers projecting both to and from the cerebellum; (2) the *middle cerebellar peduncle* is a bridge between the basilar portion of the pons and the cerebellum and is composed of fibers projecting to the cerebellum; (3) the *superior cerebellar peduncle* is a bridge between the midbrain and the cerebellum and is composed mainly of fibers projecting from the cerebellum to the brainstem and the thalamus; it also contains fibers of the anterior spinocerebellar tract projecting to the cerebellum.

SUBDIVISIONS OF THE CEREBELLUM

Hemispheres, Lobes, and Zones

The cerebellar cortex consists of two large bilateral hemispheres connected by a narrow median portion called the *vermis* (*see* **Fig. 18.1**). This transverse organization is further

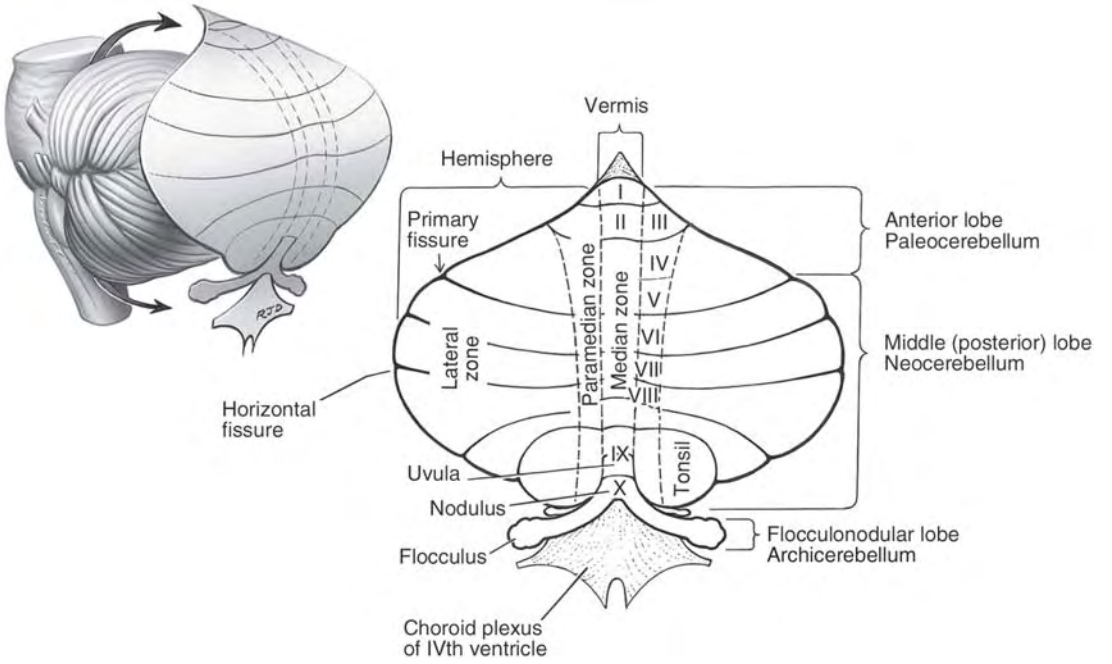


Figure 18.1: Major subdivisions and surface landmarks of the unfolded and flattened cerebellum.

subdivided into three zones: medial or vermal; paramedial, paravermal, or intermediate; and lateral or hemispheric. In addition to the cortex, each zone consists of underlying white matter and a deep cerebellar nucleus to which it topographically projects vermis to fastigial nucleus, paravermal cortex to interposed nuclei, and hemisphere to dentate nucleus (*see* **Fig. 13.11**). The cortex is characterized by the homogeneous appearance of its many gyri, called folia (leaves), generally oriented transversely and separated by sulci or fissures. There are five deep fissures. Two of these, the primary and posterolateral fissures best seen in a midsagittal section, divide the cerebellum into three lobes (*see* **Fig. 1.5**):

1. The flocculonodular lobe, behind the posterolateral fissure, consists of paired appendages called *flocculi* located posteriorly and inferiorly and joined medially by the *nodulus* (part of the vermis). It is also called the *archicerebellum* because it is phylogenetically the oldest part of the cerebellum and the *vestibulocerebellum* because this lobe is integrated with the vestibular system. The flocculonodular lobe plays a significant role in regulation of muscle tone and maintenance of equilibrium and posture through influences on the trunk (axial) musculature.
2. The *anterior lobe,* located rostral to the primary fissure, is also called the *paleocerebellum* because it is phylogenetically the next oldest part. This lobe together with the vermal and paravermal portions of the posterior lobe constitute the *spinocerebellum,* which has two somatotopic maps of the entire body surface: one in the anterior and the other in the posterior lobe (*see* **Fig. 18.2**). The spinocerebellum, which plays a role in the regulation of muscle tone, receives proprioceptive and exteroceptive inputs from the body and limbs via the spinocerebellar pathways, and from the head via fibers from the brainstem (*see* **Fig. 10.7**). The anterior lobe homunculus also receives auditory and visual inputs.

3. The large *posterior lobe* is located between the primary fissure and the posterolateral fissure. This phylogenetically newest lobe (*neocerebellum*) receives input from the cerebral cortex via a relay in the basilar pons. It performs a significant role in planning and programming of movements important for muscular coordination during phasic activities.

Cerebellar Cortex

There are three cortical layers: an outer *molecular layer*, a middle or *Purkinje cell layer* and a *granular layer* (*see* **Fig. 18.3**). The thin Purkinje layer is defined by the cell bodies of Purkinje cells. All folia have the same neuronal organization. The billions of neurons are divided into five major cell types (granule, Golgi, stellate, basket, Purkinje). A sixth type, called a "unipolar brush cells" first was identified in 1976 by Altman and Bayer and has been extensively studied in recent years.

The estimated 100 billion (10^{11}) *granule cells* are more numerous than all the neurons in the cerebral cortex. The small (5–8 μm) cell body and four to six short dendrites are all located within the granular layer; the axon projects into the molecular layer, where it bifurcates as a T into two branches (called *parallel fibers*) that course in opposite directions parallel to the long axis of the folium. Parallel fibers form excitatory synapses with dendrites of Purkinje, stellate, Golgi, and basket cells. One parallel fiber synapses with the dendrites of thousands of Purkinje cells and each Purkinje cell receives synapses from thousands of parallel fibers. Granule cells, until recently, were considered the only neurons of the cerebellar cortex whose neurotransmitter (glutamate) is excitatory. Evidence now indicates that unipolar brush cells also are glutamatergic, but their numbers, about the same as Purkinje cells, are negligible compared to granule cells.

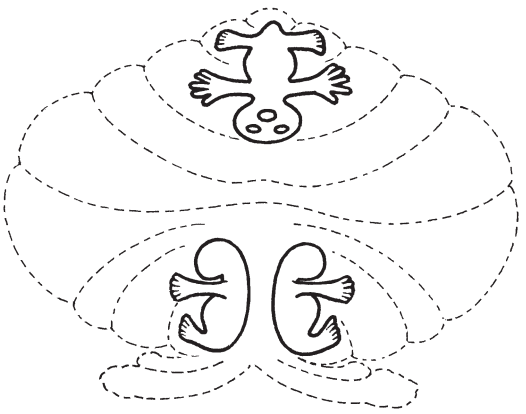


Figure 18.2: Somatotopic map of the anterior and posterior lobes of the cerebellum illustrating the somatic sensory homunculi.

Stellate cell and *basket cell somata* lie wholly within the molecular layer, the former in superficial parts of the layer and the latter in deep parts. The axon of both types is oriented at right angles to the long axis of a folium. A single stellate cell axon makes inhibitory synaptic connections with the dendrites of several Purkinje cells. Each basket cell axon forms basketlike inhibitory synaptic connections with cell bodies of several Purkinje cells. Note that because these terminals are near the initial segment of the axon where the action potential is initiated, the inhibition is very strong (Chap. 3).

Golgi cells, slightly larger (6–11 μm) than granule cells, are located near the top of the granular layer and have a cell complement equivalent to that of Purkinje cells. The dendritic tree is within the molecular layer, where it receives excitatory input from parallel fibers. The Golgi cell axon terminates within glomeruli of the granular layer by forming inhibitory synapses with dendrites of granule cells, thus forming direct feedback to the latter. A *glomerulus* (*see* **Fig. 18.3**) is a synaptic processing unit, encapsulated by a glial lamella, consisting of (1) an excitatory axon terminal of a mossy fiber, (2) dendritic endings of one or more granule cells, and (3) an inhibitory axon terminal of a Golgi cell synapsing with a dendrite of the granule cell. Dendrioles of a unipolar brush cell, not shown, also are in some glomeruli.

Unipolar brush cells also are constituents of the granular layer. Intermediate in size between granule and Golgi cells, they occur mainly in

the vestibulocerebellum and vermis. Although present in the hemispheres, their density diminishes progressively from the midline. A distinctive feature of this neuronal type is a single, short dendrite that gives rise to a spray of brushlike dendrioles that extend into a glomerulus. A single mossy fiber, in addition to terminating on granule cell dendrites, makes multiple synaptic contacts with the *dendrioles* of a unipolar brush cell (a *giant glutamatergic synapse*) in the same glomerulus, causing strong excitation. This input comes from both the vestibular nerve and vestibular nuclei, and other loci. Brush cells give rise to branching axons (intrinsic mossy fibers) that remain within the granular layer and have large terminal rosettes within other glomeruli, contacting granule cell dendrites as well as dendrioles of other unipolar brush cells, thus amplifying the effect of the extrinsic mossy fibers and potentiating vestibular signals.

Purkinje cells, which form the middle layer, provide the only output from cerebellar cortex and are its final integrating unit. The dendritic

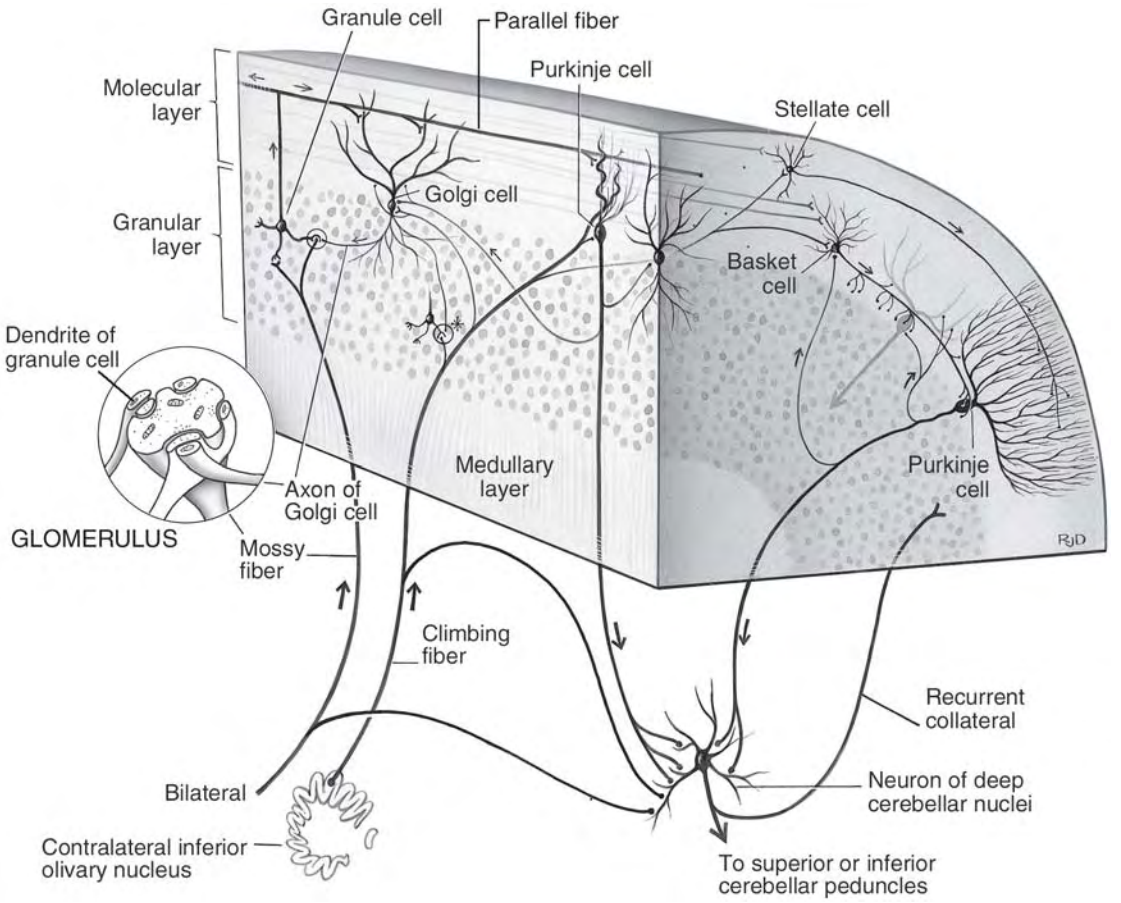


Figure 18.3: Organization and connections of the neurons within a cerebellar folium. A sagittal section through the cerebellum is represented on the right and a transverse section on the left. The long axis of a folium is in the transverse plane. The thin Purkinje cell layer, between the molecular and granular layers, is not labeled. A cerebellar glomerulus, represented in the inset, is encapsulated by a glial sheath.

tree begins at the apical end of the large goblet-shaped soma (50–80 μm) and arborizes extensively in the molecular layer in a fanlike configuration in the sagittal plane, perpendicular to the long axis of the folium (*see* **Fig. 18.3**). The dendrites are the sites of excitatory axon terminals of parallel fibers from granule cells and climbing fibers from the inferior olive and inhibitory terminations from stellate cells of the molecular layer; this is in addition to the powerful inhibitory axo-somatic synapses from basket cells. Purkinje cell axons pass into the white matter and form inhibitory synaptic connections with neurons of the deep cerebellar nuclei, releasing GABA as the neurotransmitter. The corticonuclear projection has a precise topographic organization: The medial most vermis projects to the most medial part of the fastigial nucleus, the intermediate zone projects to the interposed nucleus, and the lateral most hemisphere projects to the lateral part of the dentate nucleus. Some Purkinje cells from the archicerebellum, as well as from the vermis of the anterior and posterior lobes, emit axons that project out of the cerebellum and form inhibitory synapses with neurons of the lateral vestibular nucleus. Recurrent axon collaterals of each Purkinje cell make inhibitory connections with other Purkinje cells, basket cells, and Golgi cells. Through these inhibitory influences, the Purkinje cells modulate the output of the deep cerebellar nuclei and of the lateral vestibular nucleus. The latter exerts excitatory influences on extensor reflex activity (Chap. 16).

SALIENT FEATURES OF FUNCTION

Climbing and *mossy fibers* convey excitatory input directly from the spinal cord and brainstem, through the cerebellar peduncles, to the deep cerebellar nuclei and cerebellar cortex. The climbing fibers to each cerebellar hemisphere originate exclusively from the contralateral inferior olivary nucleus and enter the cerebellum via the inferior cerebellar peduncle (*see* **Fig. 18.3**). They exert powerful excitatory influences not only on Purkinje cells but also on cells of the deep cerebellar nuclei. Every climbing fiber divides within the granular layer into up to 10 branches (also called climbing fibers), each of which enters the molecular layer and makes up to several hundred synaptic contacts on proximal dendrites of a single Purkinje cell. Whereas collateral branches can contact several adjacent Purkinje cells, an individual Purkinje cell receives input from only one climbing fiber.

Mossy fibers originate from nuclei in the spinal cord, receptors of the vestibular nerve, and vestibular, trigeminal, pontine, and reticular nuclei of the brainstem. These fibers, which branch profusely, exert excitatory influences on numerous granule cells within glomeruli of the granular layer. Collaterals of mossy fibers, as well as of climbing fibers also can, depending on source, form excitatory synapses with the deep nuclei of the cerebellum. Through their parallel fibers, the packed granule cells make excitatory synaptic connections with the dendrites of the Purkinje cells and, in addition, with dendrites of stellate cells, basket cells and Golgi cells in the molecular layer. After excitation, the stellate and basket cells, exert inhibitory influences on Purkinje cells. Similarly, the Golgi cells inhibit the granule cells within the glomeruli.

The following is an account of how the output from the cerebellar cortex is orchestrated. Purkinje cells, through their axons, are the only outlets for processed information from the cerebellar cortex. Their output, directed to the deep cerebellar nuclei and the lateral vestibular nucleus, is solely inhibitory. Insofar as mossy and climbing fibers supply only excitatory inputs, it is the Purkinje fibers that modulate, through inhibition, the output from the deep cerebellar nuclei to targets outside the cerebellum (and output from the lateral vestibular nucleus). As mentioned, Purkinje cells are excited as well as inhibited by stimuli from other cells. The climbing fibers and granule cells contribute excitatory influences; the stellate and basket cells convey inhibitory stimuli.

A final element of this mosaic concerns the granule cells. Granule cell output is modulated

by excitatory input from unipolar brush cells (mainly in the vestibulocerebellum and vermis) and inhibitory influences from Golgi cells. The latter in turn depend on granule cells for their own activation. This negative feedback circuit consists of the sequence (1) granule cell, (2) Golgi cell, and (3) Golgi cell axon that extends back to form inhibitory synapses on granule cells within glomeruli.

In summary, the wholly excitatory input to the cerebellum is via mossy and climbing fibers. Of the neurons whose cell bodies are located within the cerebellar cortex, the granule cells are the only excitatory ones whose axons leaves the layer of origin. Although unipolar brush cells also are excitatory, their axons are restricted to the granular layer where they increase the excitation upon granule cells. The Golgi, Purkinje, stellate, and basket cells are inhibitory neurons, whose neurotransmitter is GABA. They act as modulators. The cerebellar nuclei also convey excitatory input to the granular layer of cerebellar cortex via nucleocortical connections, some of which are collaterals of fibers that project out of the cerebellum.

In addition, aminergic cell groups such as the locus ceruleus and raphe nuclei of the brainstem provide another input to the cerebellum. Their projections terminate in the deep cerebellar nuclei and the cerebellar cortex, including from the locus ceruleus directly on Purkinje cell somata. The projections from the locus ceruleus are noradrenergic and those from the raphe nuclei are serotonergic. Input from these sources is thought to have generalized effects on the tone of cerebellar activity.

GENERAL CEREBELLAR CIRCUITRY

Input to the Cerebellum

There are approximately three times as many cerebellar afferent fibers as there are cerebellar efferent fibers.

The *inferior cerebellar peduncle (restiform body)* is composed of fibers of the posterior spinocerebellar tract, cuneocerebellar tract, rostral spinocerebellar tract, reticulocerebellar fibers, olivocerebellar fibers, and trigeminocerebellar fibers. The *juxtarestiform body* (bundle of fibers on medial aspect of the inferior cerebellar peduncle) contains vestibulocerebellar fibers from both the vestibular nuclei and the vestibular nerve (Chap. 16). The posterior spinocerebellar, cuneocerebellar, and rostral cerebellar tracts convey information from stretch and exteroceptive receptors of the body via the spinal cord to the anterior lobe of the cerebellum (Chap. 10). Reticulocerebellar fibers project from the lateral reticular nucleus of the medulla (input to this nucleus is from the spinal cord, red nucleus, and fastigial nucleus) and paramedian nuclei of the medulla, largely as uncrossed components, to the anterior lobe and vermis. Olivocerebellar fibers originate in the contralateral inferior olivary nucleus of the medulla and terminate in all cortical areas of the cerebellum. The accessory olivary nuclei project to the vermis, and the principal olivary nucleus projects to the opposite cerebellar hemisphere. Input to the inferior olivary nuclei is derived from the cerebral cortex, brainstem reticular nuclei, dorsal column nuclei, red nucleus, and spinal cord, as well as from the cerebellum. The *inferior olivary nucleus* is the only source of climbing fibers to the cerebellum. The trigeminocerebellar fibers convey influences from stretch and exteroceptive receptors of the head. Primary fibers from the vestibular nerve and secondary fibers from vestibular nuclei pass, as vestibulocerebellar fibers, through the juxtarestiform body before terminating in the flocculonodular lobe and adjacent cortex (referred to as the *vestibulocerebellum*). Secondary but not primary vestibular fibers emit collaterals to the fastigial nuclei as well.

The *middle cerebellar peduncle (brachium pontis)* is composed of crossed pontocerebellar fibers projecting from the pontine nuclei in the basilar pons to the neocerebellum and paleocerebellum. This tract conveys influences from the cerebral cortex transmitted via the corticopontine tract.

The *superior cerebellar peduncle (brachium conjunctivum)* contains fibers of the anterior

spinocerebellar tract, which terminate in the anterior lobe (*see* **Fig. 13.13** and Chap. 10).

Output From the Cerebellum

The cerebellum influences motor coordination almost entirely through indirect pathways (*see* **Figs. 18.4 and 18.5**). There is evidence supporting the presence of a small projection directly to the spinal cord. The main output from the cerebellum consists of separate fiber systems that arise from the three pairs of cerebellar nuclei (fastigial, interposed, and dentate) and have excitatory influences on their targets. Purkinje cells from the vestibulocerebellum and entire vermis in part emit axons that leave the cerebellum and directly inhibit the vestibular nuclei.

The outflow through the juxtarestiform body includes (1) crossed and uncrossed fastigiobulbar fibers from the fastigial nuclei to the vestibular nuclei and reticular nuclei of the pons and medulla, (2) a few fibers that synapse monosynaptically on lower motoneurons in the contralateral upper cervical spinal cord, and (3) some direct fibers from the cortex of the vestibulocerebellum (flocculonodular lobe) and throughout the vermis to the vestibular nuclei. Some fibers from the fastigial nuclei pass around the rostral aspect of the superior cerebellar peduncle as the *uncinate (hooked) fasciculus* before passing through the juxtarestiform body (*see* **Figs. 13.11 and 18.5**). Each fastigial nucleus receives input from the vestibular nuclei and cortex of the archicerebellum.

The *superior cerebellar peduncle* consists primarily of efferent fibers from the dentate, emboliform, and globose nuclei. Those arising from the large dentate nucleus are called the dentatorubral, dentatothalamic, and dentatoreticular tracts. The entire outflow crosses to the opposite side in the lower midbrain as the decussation of the superior cerebellar peduncle. Most fibers from the dentate nucleus project rostrally to the ventral lateral and intralaminar thalamic nuclei, with some fibers terminating in the rostral (parvocellular) third of the red nucleus, which gives rise to the rubroolivary tract. Other fibers turn caudally as the *descending branch of the superior cerebellar peduncle* to terminate in the brainstem reticular nuclei (reticulotegmental nucleus) as well as the principal inferior olive. The interposed nuclei project to the caudal (magnocellular) part of the red nucleus, which is the source of the rubrospinal tract. Descending postdecussational fibers go to brainstem reticular nuclei, some to the dorsal and medial accessory olives, and a few to the upper cervical spinal cord, where they terminate upon interneurons in the intermediate gray.

FUNCTIONAL CONSIDERATIONS

The cerebellum, as indicated, can be divided into four anatomic zones: (1) median zone or vermis, (2) paramedian or intermediate zone, (3) lateral zone or lateral hemisphere, and (4) floccular–nodular lobe or vestibulocerebellum (*see* **Fig. 18.1**). Three recognized functional divisions include the (1) *spinocerebellum*, which comprises the anterior lobe and the median and paramedian zones of the posterior lobe, (2) *cerebrocerebellum*, which comprises the lateral zone, and (3) *vestibulocerebellum* or the flocculonodular lobe.

The spinocerebellum is involved in the control of movements of the body axis (posture) and primarily proximal limbs. It receives somatosensory input from the spinal cord, providing details about the progress of ongoing movements, and generates information to correct errors. The cerebrocerebellum receives strong input from the cerebral cortex and is involved in the planning of movement and learning of sequences in complex movements such as playing a piano. The vestibulocerebellum receives input from the vestibular receptors and is involved in the maintenance of balance and regulation of head and eye movements. It is important to realize that these circuits are indicative of the complex anatomic circuitry by which the cerebellum is integrated into the control of motor activity of the muscles of the body.

These functional divisions of the cerebellar cortex have similar patterns in the organization of their intrinsic circuitry, as described previ-

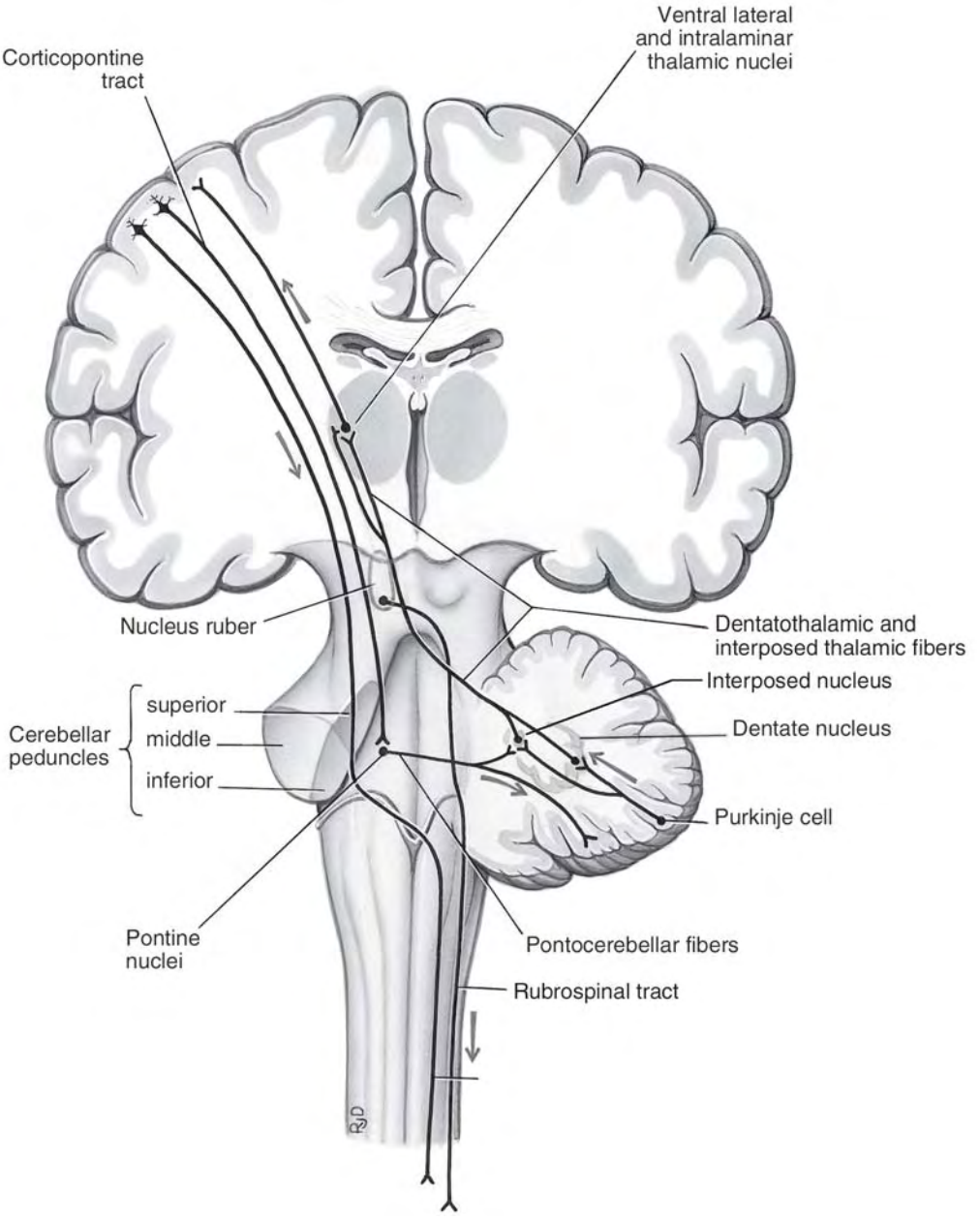


Figure 18.4: Cerebellar (neocerebellar) connections with the cerebral cortex, thalamus and some brainstem nuclei.

ously in this chapter. Each division differs, however, from the others with respect to the specific sources of afferent input and the specific neural centers to which it projects.

Each of the circuits outlined below is organized to become involved in specific aspects of the functional control of certain muscle groups. In brief, the vermis is associated with the

control of axial muscles, the intermediate hemisphere is associated with the control of limb muscles, the cerebrocerebellum is associated with the planning of movement, and the vestibulocerebellum is associated with the maintenance of balance and control of eye movements. Recall that the deep cerebellar nuclei receive excitatory input from the climbing fibers, which originate from the inferior olivary nucleus. Note that these circuits are organized to relay their influences selectively to either the medial or lateral descending motor systems (Chap. 8).

Circuitry Associated With the Vermis (Vermal Zone)

Somatic sensory information from the body and limbs is conveyed somatotopically via the dorsal spinocerebellar and cuneocerebellar tracts to the cortex of the vermis (*see* **Fig. 18.2** and Chap. 10). In addition, afferent input from the head is derived from the spinal trigeminal nucleus and vestibular, auditory, and visual systems. The vermal cortex projects to the fastigial nucleus, which, in turn, projects to two different regions via fibers passing through the inferior cerebellar peduncle. (1) The largest number of fibers terminate in the vestibular nuclei and a substantial group descends in the juxtarestiform body and central tegmental tract of the brainstem to pontine and medullary reticular nuclei. (2) A few fibers ascend and terminate mainly in the contralateral ventral lateral (VL) nucleus of the thalamus. Projections from this part of the VL ascend and terminate in the regions of the primary motor cortex, which give rise to the anterior corticospinal tract. The pontine and medullary reticular

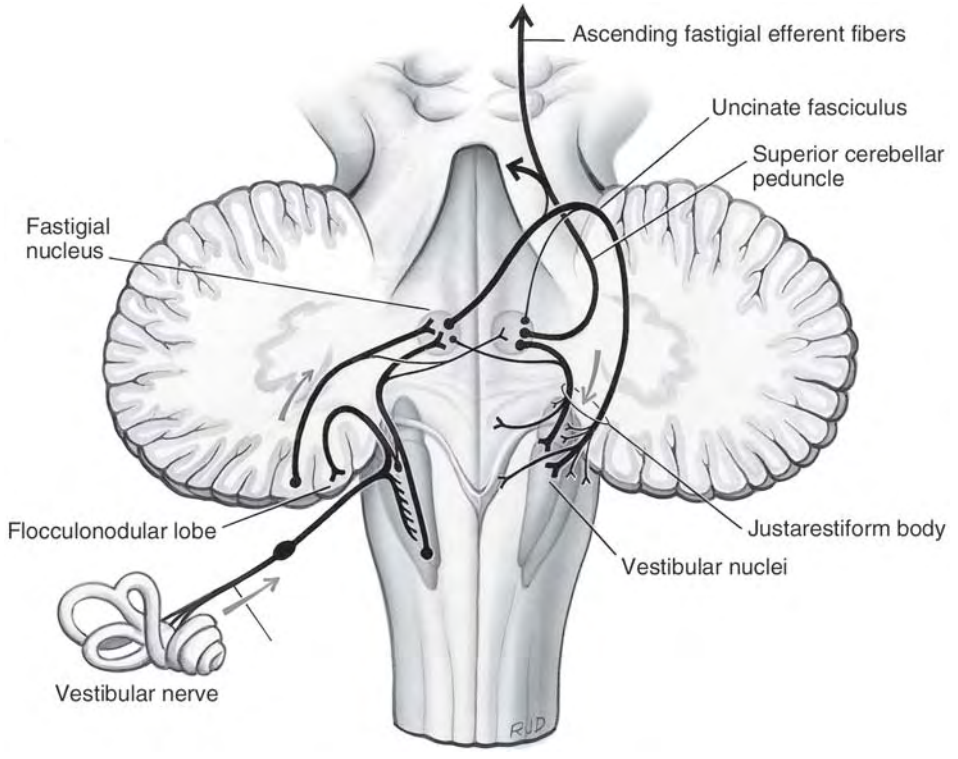


Figure 18.5: The vestibulocerebellar pathways. Left: input to the cerebellum; right: output from the cerebellum.

nuclei give rise respectively to the medial and lateral reticulospinal tracts. All three of these tracts belong to the *medial descending systems* (Chap. 11), which terminate in the medial column of spinal gray matter where lower motoneurons innervating axial musculature are located. *Note the linkage between the vermis (vermal zone) and the control of the axial and girdle musculature*. Purkinje cells in the vermis also project to the ipsilateral lateral and inferior vestibular nuclei

Circuitry Associated With Intermediate Hemisphere (Paravermal Zone)

Somatic sensory information is conveyed via the dorsal spinocerebellar and cuneocerebellar tracts to the cortex of the intermediate lobe (Chap. 10). This cortex projects to the interposed nuclei, which give rise to fibers that pass through the superior cerebellar peduncle and cross in the decussation of the superior cerebellar peduncle. Some fibers terminate in the magnocellular portion of the red nucleus. Others ascend and terminate in the VL. The ventrolateral nucleus projects to the primary motor cortex (area 4) and the supplementary motor cortex (area 6). The *lateral descending system* originates from these sources, the rubrospinal tract originates from the magnocellular portion of the nucleus ruber, and the lateral corticospinal tract originates from the primary motor and supplementary cortices. These tracts control the activity of the musculature of the extremities. *Note the linkage between the intermediate hemisphere and control of musculature of the extremities*.

Circuitry Associated With the Cerebrocerebellum (Lateral Hemisphere or Zone)

The cerebellar hemispheres are reciprocally interconnected with the cerebral cortex. The output originates from many areas of the cerebral cortex, but largely from the motor cortices (areas 4 and 6) and the somatic sensory cortices (areas 1, 2, 3, and 5). These projections comprise the corticopontine fibers that pass successively through the posterior limb of the internal capsule, the crus cerebri of the midbrain, and terminate in the ipsilateral pontine nuclei. These nuclei give rise to pontocerebellar fibers, which decussate and form the middle cerebellar peduncle; they terminate in the contralateral cerebellar cortex of the lateral hemisphere. Axons of Purkinje cells arising from this cortex project to the dentate nucleus. This nucleus gives rise to fibers that course through the superior cerebellar peduncle to two different structures. (1) Some fibers contribute to the following circuit: They cross in the decussation of the superior cerebellar peduncle and terminate in the contralateral parvocellular division of the red nucleus, which gives rise to the rubroolivary fibers that terminate in the inferior olivary complex. A few postdecussational fibers in the peduncle turn caudally and go directly to the inferior olivary complex. This complex is the source of olivocerebellar fibers that decussate and enter the inferior cerebellar peduncle to terminate as climbing fibers. The inferior olive is the only source of climbing fibers; they terminate and synapse with neurons in both the deep cerebellar (fastigial, interpositus and dentate) nuclei and axodendritically on Purkinje cells of the cerebellar cortex. (2) The largest number of fiber crosses over in the decussation of the superior cerebellar peduncle and ascends to the thalamus where they terminate in VL. This nucleus projects to primary motor cortex and premotor cortex. The primary motor cortex gives rise to the lateral corticospinal tract of the *lateral descending system* and anterior corticospinal tract of the *medial descending system*. The premotor cortex gives rise to corticoreticular fibers to the pontine and medullary reticular nuclei, which give rise to the medial and lateral reticulospinal tracts of the *medial descending system. Note the linkage between the lateral hemispheric zone and the cerebrum for the planning of movement*.

Circuitry Associated With the Vestibulocerebellum (Flocculonodular Lobe)

The input to the vestibulocerebellar cortex is derived from the vestibular nuclei and directly from the vestibular labyrinth via some fibers of

the vestibular nerve, the only primary fibers to enter the cerebellum. Purkinje cell axons from this cortex project ipsilaterally to the fastigial nucleus and to the medial, inferior, and superior vestibular nuclei. Cortex of the uvula, which can in terms of connectivity be considered as part of the vestibulocerebellum, also sends fibers to the lateral vestibular nucleus. The projections to the vestibular nuclei (the only projections from the cerebellar cortex to a noncerebellar site) indicate that these nuclei are similar to deep cerebellar nuclei. The medial vestibular nucleus gives rise to the medial vestibulospinal tract of the *medial descending system*. A few fibers from the fastigial nucleus ascend and pass through the superior cerebellar peduncle and terminate in the contralateral VL nucleus. These VL neurons project to those sites of primary motor cortex that give rise to the anterior corticospinal tract of the *medial descending system. Note the linkage between the flocculonodular lobe and the axial musculature* (*see* discussion of the vestibular system in Chap. 16).

Thalamic Projections of the Cerebellar Nuclei

As noted, the dentate, interposed, and fastigial nuclei all project to the ventrolateral nucleus of the thalamus. Fibers originating from these nuclei terminate in a relatively acellular zone sandwiched between, and separate from, the projection fields of the somatosensory pathways and of the basal ganglia in the ventral posterior and ventral anterior nuclei, respectively. The entirely crossed terminations from the dentate and interposed nuclei are separate but interdigitating. The small number of fibers from the fastigial nucleus is distributed bilaterally to a more limited region. This indicates that the functional differences of the cerebellar zones are retained at thalamic levels. The cerebellar nuclei also project to the intralaminar group of the thalamic nuclei.

Internal Feedback Connections to the Cerebellum

The anterior spinocerebellar and the rostrocerebellar tracts that terminate in the vermis (Chap. 10) probably do not relay sensory information derived from the periphery to the cerebellum. Rather, these tracts are thought to be in an *internal feedback circuit* to the cerebellum. These nuclei can be monitoring neural activity of the descending motor pathways and then informing the cerebellum.

Postulated Role of Cerebellum in Cognitive and Language Function

The presence of reciprocal connections between phylogenetically new cerebellar structures (ventrolateral parts of the dentate nucleus, referred to as neodentate, and some of the lateral lobe cortex) and the frontal association areas of the cerebral cortex suggest that the cerebellum has a role in cognitive function. Evidence from imaging studies (magnetic resonance imaging [MRI] and positron-emitting tomography [PET]) support the view that the "computational power of the cerebellum" is used for some nonmotor activities such as puzzle solving and language processing. Deficits in the latter and in error detection have been reported in cases with unilateral cerebellar damage documented by PET.

CEREBELLAR DYSFUNCTION

The cerebellar cortex participates in mechanisms of motor function via the Purkinje cells, which modulate the level of excitability of the deep cerebellar nuclei and their output. The delicate and subtle interactions of the cerebellar cortex with the deep nuclei are basic to the precision, speed, and coordination essential for motor activities. These are expressions of *synergy*—the cooperative activity of all the muscles utilized in each motor act.

Injury to the cerebellum or its afferent/efferent pathways eliminates cerebellar influences on structures important for control of motor activity. This causes so-called *release phenomena* that are expressions of the loss of negative feedback. For instance, a *tremor* occurs when moving the upper extremity to touch an object with a finger and the arm oscillates back and forth as the tip of finger approaches the object.

In the normal cerebellum, negative feedback activity reduces each overshoot to insignificance, like an automatic pilot in an airplane. Thus, the cerebellum acts as a servomechanism in a negative feedback system, functioning to prevent oscillations (tremor) during motion and thereby maintaining stability in a movement.

Unilateral cerebellar lesions have *ipsilateral effects*. Symptoms are expressed on the same side of the body because the pathways from the cerebellum decussate and integrate with pathway systems that, in turn, cross over to the side of the original cerebellar output to exert their effects. For example, one side of the cerebellum projects via the crossed dentatothalamocortical pathway to the contralateral red nucleus and cerebral cortex. In turn, the rubrospinal and corticospinal tracts are crossed descending pathways. In effect, the cerebellum exerts its influences through a double-crossing of (1) the ascending fibers of the decussating superior cerebellar peduncle and (2) the decussating descending rubrospinal and corticospinal tracts.

Lesions of the cerebellum result in disturbances expressed as a *constellation* of symptoms and neurological signs. Cerebellar cortex possesses a good margin of physiologic safety; with sufficient time, the neurologic symptoms attenuate, and the resulting compensation, presumably by other mechanisms in the brain, markedly reduces the severity of the deficits. Small lesions can produce no symptoms or only transient ones, whereas large lesions produce severe symptoms. Disturbances following cerebellar lesions are related to the site of pathology, which, in many instances, is not restricted to one subdivision. Lesions of the neocerebellum interfere with pathways channeled toward corticospinal and associated pathways and, thus, selectively affect skilled movements. Lesions of the archicerebellum whose output goes to medial descending motor systems cause disturbances of equilibrium and balance.

Neocerebellar Lesions

Neocerebellar in the context of lesions refers to both the cortex of the hemisphere and the underlying dentate and interposed nuclei. With neocerebellar lesions, tendon reflexes are diminished (*hypotonia*); this effect is expressed as a pendular knee jerk that swings freely back and forth. Muscles tire easily (*asthenia*). An arm extended horizontally gradually drifts downward when the eyes are closed because proprioceptive sense is used improperly. *Asynergia*, or loss of muscular coordination, is expressed by jerky, puppetlike movements, including the decomposition of movement, dysmetria, past-pointing, and dysdiadochokinesis.

Decomposition of movement is the breaking up of a movement into its component parts; instead of a smooth, coordinated flow of movement in bringing the tip of the finger of the extended upper extremity to the nose, each joint of the shoulder, elbow, wrist, and finger might flex independently (puppetlike) in an almost mechanical fashion. *Dysmetria*, or the inability to gauge or measure distances accurately, results in the overshooting of an intended goal by consistent pointing toward the lesion side of the object *(past-pointing). Dysdiadochokinesis* is the impairment of the ability to execute alternating and repetitive movements, such as supination and pronation of the forearm, in rapid succession with equal excursions. *Tremor* is expressed during the execution of a voluntary movement. It is absent or diminished during rest. Such a tremor, which is displayed during movements but not at rest, is referred to as a cerebellar or intention tremor.

An ataxic gait, or the asynergic activity elicited during walking, is a staggering movement resembling that of drunkenness. The ataxia is a result of incoordination of the trunk and proximal girdle muscles. A tendency to veer or to fall to the side of the lesion is apparent. To counteract the unsteadiness, a patient will stand or walk with legs far apart (broad-based stance). Clinicians usually equate asynergy with ataxia.

Lack of check (rebound phenomenon) is demonstrable in neocerebellar lesions. Lack of check is the inability of a rapidly moving limb, to stop quickly and sharply; in the attempt to stop the limb there is an overshoot and then a

rebound (overshoot in the opposite direction). For example, the forearm is flexed at the elbow against a strong resistance exerted by the examiner; when the examiner suddenly removes the resistance, the forearm jerks forward and the subject is unable to check the motion before the hand strikes the chest.

A *scanning speech*, or *dysarthria*, occurs because of an incoordination of the muscles used in speaking. The speech is hesitating, slurred, and explosive in quality, with a telegraph-staccato pace (pauses in the wrong places). Although the mechanisms of speech are impaired, there is no aphasia (Chap. 25). However, there do appear to be disturbances in verbalization and some aspects of reasoning.

Lesions of the Archicerebellum and Vermis of the Anterior and Posterior Lobes

The archicerebellum consists of the flocculonodular lobe of which the nodulus is part of the vermis. The remainder of the vermis of the anterior and posterior lobes is closely related to the flocculonodular lobe in that Purkinje cells project to the fastigial nuclei as well as directly to the lateral and other vestibular nuclei; the entire vermis receives input from the vestibular complex.

Lesions of the archicerebellum and other parts of the vermis produce disturbances in stance and gait. The patient stands and walks with feet several inches apart (broad-based gait) and has difficulty in placing the heel of one foot in front of the other in a sequential order (impairment *of tandem gait*). *Titubation,* a rapid rhythmic tremor of the head or body, can occur, sometimes accompanied by nystagmus (rhythmic oscillation of the eyes).

Cortical degeneration affecting the vermis of the anterior and posterior lobes is seen in some alcoholic patients. Disturbances involve the lower limbs and gait, which is ataxic and wide based. Asynergia of the lower limbs can be demonstrated by the *heel–shin test* in which the heel of one foot is made to slide down the shin of the opposite leg.

Lesions involving the flocculonodular lobe and uvula can result in ataxia of the trunk muscles without any signs of tremor or hypotonia. Children with nodular lobe tumors have a tendency to fall backward, sway from side to side, and walk with a wide base and an ataxic gait. They might be unable to maintain an upright balance.

Neurodegenerative Diseases Affecting the Cerebellum

Cerebellar ataxia together with dementia is distinguished by a spongiform degeneration of cortical neurons in the cerebellum and cerebrum. Degeneration coupled with marked glial proliferation cytoplasmic vacuoles is referred to as spongiform. The main clinical signs are cerebellar ataxia and progressive dementia. Diseases expressing these manifestations include Kuru, documented in New Guinea where human brains were eaten while preparing bodies for burial, Creutzfeldt–Jacob disease, shown to be transmittable, scrapie, a disease found in sheep, and mad cow disease. All of these related diseases appear to be caused by modifications of the conformation of proteins called “prions” (Prusiner, 1998).

SUGGESTED READINGS

Altman J, Bayer SA. Time of origin and distribution of a new cell type in the rat cerebellar cortex. *Exp. Brain Res.* 1977;29:265–274.

Dino MR, Schuerger RJ, Liu Y, Slater NT, Mugnaini E. Unipolar brush cell: a potential feedforward excitatory interneuron of the cerebellum. *Neuroscience* 2000;98:625–636.

Gebhart AL, Petersen SE, Thach WT. Role of the posterolateral cerebellum in language. *Ann. NY Acad. Sci.* 2002;978:318–333.

Gerrits NM, Ruigrok TJH, de Zeeuw CI, eds. *Cerebellar Modules: Molecules, Morphology, and Function.* New York: Elsevier; 2000.

Glickstein M. The cerebellum and motor learning. *Curr. Opin. Neurobiol.* 1992;2:802–806.

Hua SE, Houk JC. Cerebellar guidance of premotor network development and sensorimotor learning. *Learn. Mem.* 1997;4:63–76.

Ito M. *The Cerebellum and Neural Control.* New York: Raven; 1984.

Ito M. Synaptic Plasticity in the cerebellar cortex and its role in motor learning. *Can. J. Neurol. Sci.* 1993;20(Suppl. 3):S70–S74.

Kelly RM, Strick PL. Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. *J Neurosci.* 2003;23:8432–8444.

Leiner HC, Leiner AL, Dow RS. Cognitive and language functions of the human cerebellum. *Trends Neurosci.* 1993;16:444–447.

Llinás RR, Sotelo C, eds. *The Cerebellum Revisited.* New York: Springer-Verlag; 1992.

Manto M-U, Pandolfo M. *The Cerebellum and its Disorders.* Cambridge: Cambridge University Press; 2002.

Middleton FA, Strick PL. Basal ganglia and cerebellar loops: motor and cognitive circuits. *Brain Res Brain Res. Rev.* 2000;31:236–250.

Miller LE, Holdefer RN, Houk JC. The role of the cerebellum in modulating voluntary limb movement commands. *Arch. Ital. Biol.* 2002;140: 175–183.

Nunzi MG, Birnstiel S, Bhattacharyya BJ, Slater NT, Mugnaini E. Unipolar brush cells form a glutamatergic projection system within the mouse cerebellar cortex. *J. Comp. Neurol.* 2001;434: 329–341.

Prusiner SB. Prions. *Proc. Natl. Acad. Sci. USA* 1998;95:13363–13383.

Raymond JL, Lisberger SG, Mauk MD. *The cerebellum: a neuronal learning machine? Science.* 1996;272:1126–1131.

Robinson FR. Role of the cerebellum in movement control and adaptation. *Curr. Opin. Neurobiol.* 1995;5:755–762.

Thach WT. A role for the cerebellum in learning movement coordination. *Neurobiol. Learn. Mem.* 1998;70:177–188.

Thach WT, Bastian AJ. Role of the cerebellum in the control and adaptation of gait in health and disease. *Prog. Brain Res.* 2004;143:353–366.

Thompson RF, Kim JJ. Memory systems in the brain and localization of a memory. *Proc. Natl. Acad. Sci. USA* 1996;93:13438–13444.

Voogd J. The human cerebellum. *J. Chem. Neuroanat.* 2003;26:243–252.

Voogd J, Glickstein M. The anatomy of the cerebellum. *Trends Neurosci.* 1998;21:370–375.

Zagon IS, McLaughlin PJ, Smith S. Neural populations in the human cerebellum: estimations from isolated cell nuclei. *Brain Res.* 1977;127: 279–282.

Zeeuw Cide, Strata P, Voogd J. *The Cerebellum: From Structure to Control.* New York: Elsevier; 1997.

19
The Visual System

Anatomy of the Eye
Retina
Topographic (Retinotopic) Representation of the Visual Fields
Retinogeniculostriate Pathway
Visual Cortex
The M (Magnocellular) and P (Parvocelllar) Pathways
Reflex Pathways
Control of Eye Movements
Lesions of the Visual Pathways

We live largely in a visual world and yet our eyes can detect only a small part of the broad spectrum of electromagnetic radiation engulfing us. The eyes are sensitive only in the wavelengths of the visual spectrum ranging from 400 to 700 nm, i.e., from blue to red. Signals from the eyes are transmitted centrally via several pathways or channels reflecting different functional aspects of vision. The visual system analyses such features as color, brightness, form or detail, three-dimensionality, location and motion of an object.

ANATOMY OF THE EYE

The eye is a globe composed of three layers (*see* **Fig. 19.1**). The posterior five-sixths of the outer layer consists of the tough fibrous sclera; the transparent cornea covers the anterior part. The middle layer consists of the vascularized choroid, the ciliary body and iris. The retina forms the inner layer. The neural portion of the retina at the back of the eye contains the sensory receptors (rods and cones). The non-neural portion consists of the unpigmented epithelium of the ciliary body and the pigmented epithelium at the back of the iris. The lens, located behind the iris diaphragm, is suspended by fine "guy ropes" called *zonula fibers* that encircle it and are anchored in the folds of the ciliary body.

The cornea is a nonadjustable lens of the eye, whereas the lens proper is adjustable. The ciliary body contains involuntary muscles that vary the tension exerted on the lens by the zonula fibers. Their contraction alters the shape and, thus, refractive power of the lens called *accommodation*. The inner part of the ciliary body, called the *ciliary processes*, secretes the aqueous humor, which circulates through and fills the anterior and posterior chambers of the eye. The aqueous humor is returned to the venous circulation by diffusing through a trabecular network located deep to the iridocorneal angle of the anterior chamber (*see* **Fig. 19.1**).

The iris diaphragm surrounds the pupil. The contractile state of the smooth muscles of the iris results in the enlargement or reduction in the diameter of the pupil and thereby regulates the amount of light passing into the depths of the eye. Contraction of the radial muscles of the iris results in dilation of the pupil. Contraction of the circular (sphincter) muscles causes pupillary constriction.

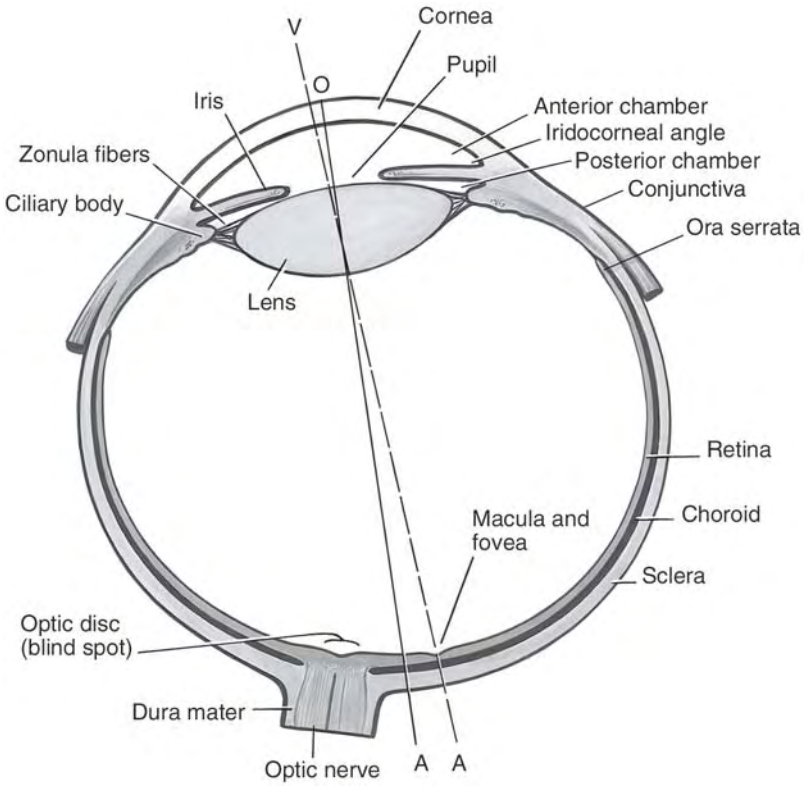


Figure 19.1: Horizontal equatorial section through the human right eye. The visual axis (VA) is the line joining the fixation or "nodal" point (center of object in focus) within the lens with the fovea. The optical axis (OA) is the line passing through the optical centers of the principal refracting surfaces, the cornea, and lens.

RETINA

Light passes through the cornea, lens, and two fluids—the *aqueous humor* in the anterior chamber between the cornea and the lens and the *vitreous humor* between the lens and the retina—to reach the retinal photoreceptors (*see* **Fig. 19.1**). The aqueous humor is a clear watery fluid that supplies nutrients to the avascular cornea and lens. The vitreous humor is a moderately turgid gelatinous substance that is actually a form of connective tissue (98% water, 2% collagen and hyaluronic acid) composed of a network of collagen fibrils. It constitutes 80% of the volume of the eyeball and maintains its shape. The vitreous becomes more fluid with age; the mass decreases and can detach from the retina. Collapse of the vitreous humor leads to release of fibrous densities called floaters or muscae volitantes (flying flies)—compressed strands of gel and other debris that can interfere with vision and be bothersome.

The neural retina is part of the central nervous system (CNS). Its five cell types include photoreceptor (*rods and cones), bipolar, horizontal, amacrine,* and *ganglion cells* (*see* **Fig. 19.2**). Anatomically, the photoreceptor, bipolar, and ganglion cells are vertically oriented sequentially within the retina. This forms a direct functional pathway for "*vertical information flow"* to the brain. In contrast, the horizontal and amacrine cells are horizontally oriented for "*lateral information flow"* within

the retina. The *macula* is a yellowish spot (3 mm in diameter) in the middle of the retina with relatively few blood vessels, in the middle of which is the 0.4-mm *fovea centralis* containing only cone receptors (*see* **Fig. 19.1**). Cones diminish toward the peripheral part of the retina, where there are only rods.

The panorama seen by both eyes, fixed on one point at a single moment, is called the *visual field*. Quanta of light called photons enter the eyes to stimulate the photopigments in the disks of the outer segments of the *rods* and *cones* (*see* **Fig. 19.3**).

Rods and Cones

Transduction in the photon-absorbing photopigment triggers activation of a G-protein (transducin) and, in turn, a second-messenger biochemical cascade that regulates the opening and closing of the c-GMP (guanosine monophosphate) ion channels of the membrane of the outer segment of the rods and cones (*see* **Fig. 19.3**). All rods contain the photopigment rhodopsin, which is sensitive to a broad range of the visual spectrum with maximal absorption at 495 nm. Rhodopsin mediates vision in dim light. There are three types of cone, each

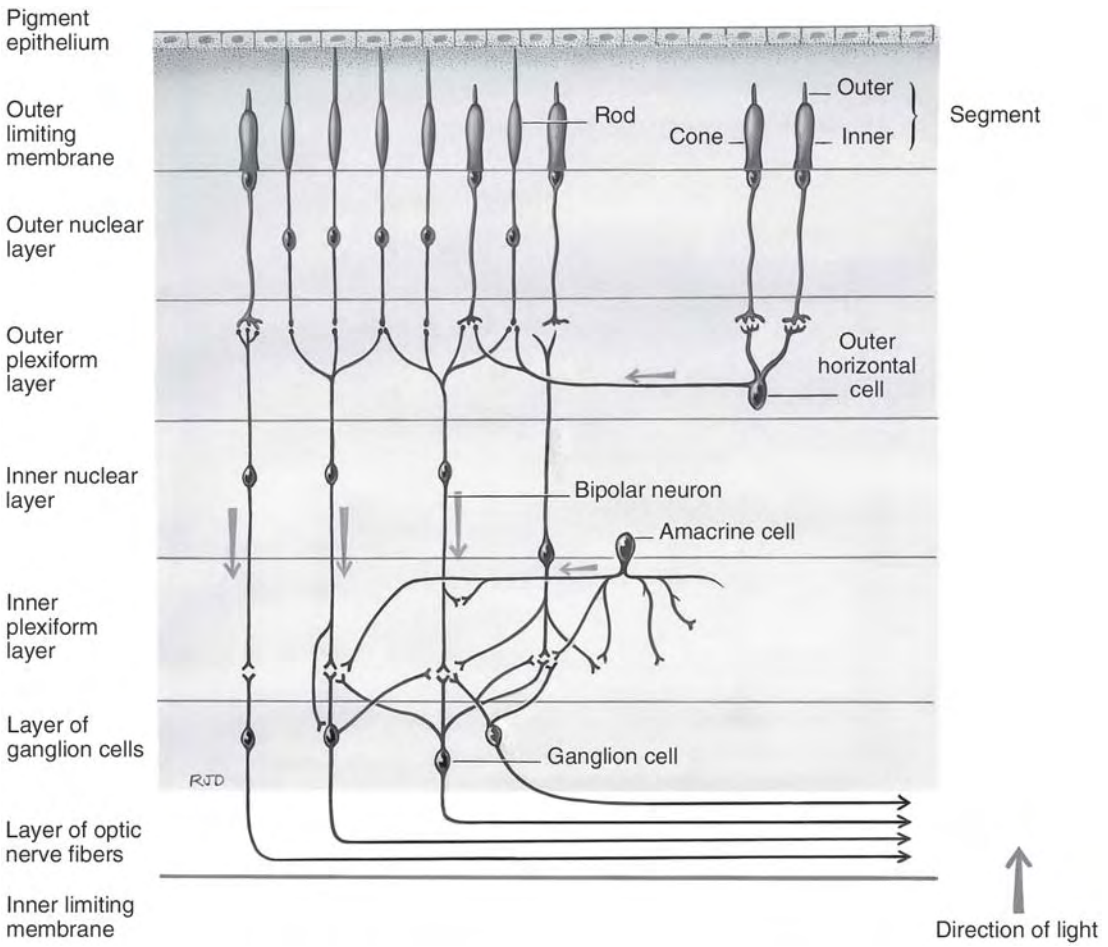


Figure 19.2: Laminar and cellular organization of the retina.

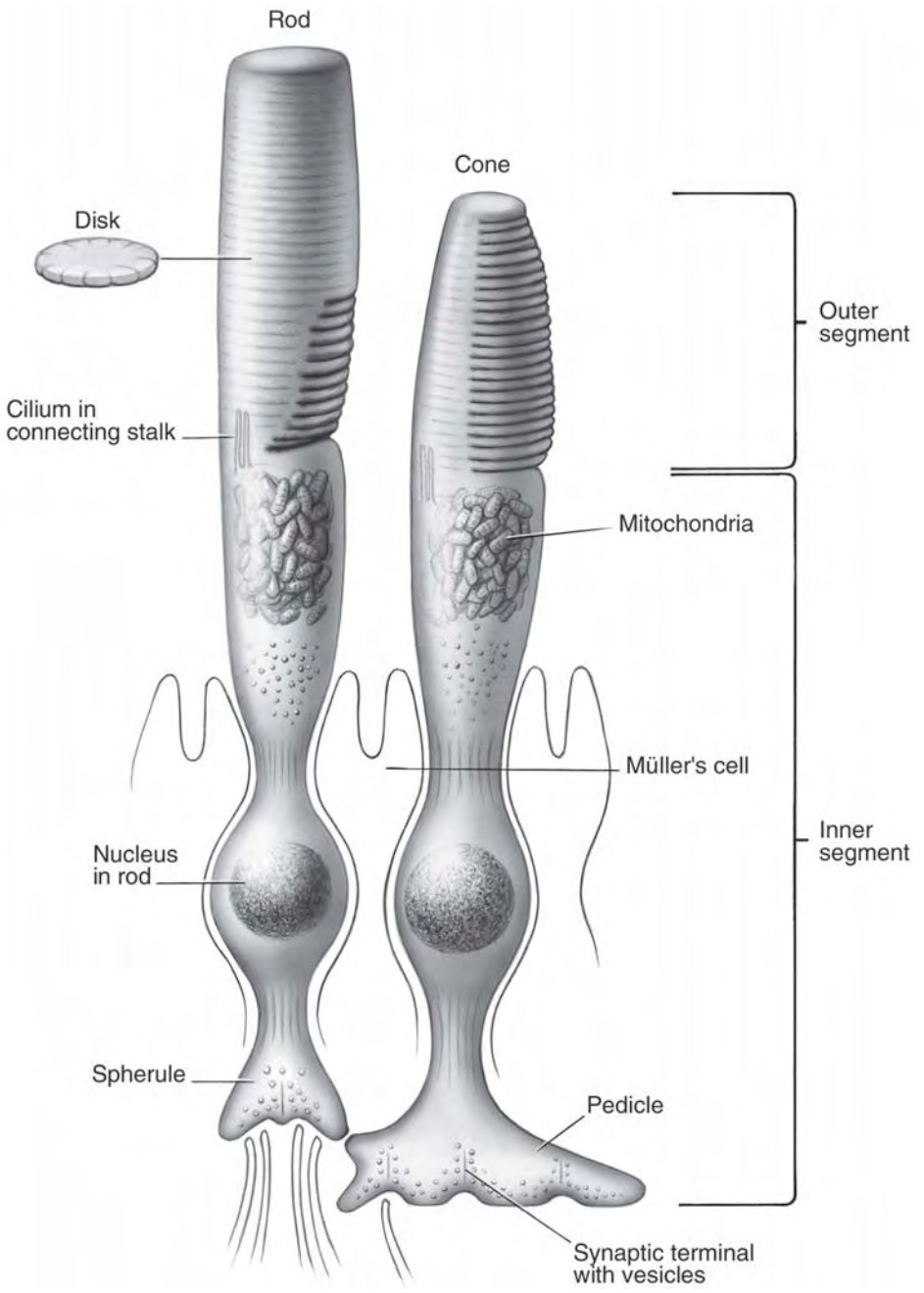


Figure 19.3: A rod and a cone. Each rod (or cone) consists of an outer segment and an inner segment connected by a cilium. The outer segment of the rod is rod shaped and that of the cone is cone shaped. In both, the receptor disks are specialized structures of the plasma membrane that contain the photopigments (integral proteins). The new disks of a rod are continuously formed by repeated infolding of the plasma membrane at the base of the outer segment. The disks of the cones are not continuously replaced. The inner segment contains biosynthetic organelles and synaptic terminals.

with a photopigment sensitive to different wavelengths of light, named *short- (blue), medium- (green), and long- (red) wavelength cones*.

The rods and cones generate separate parallel processing pathway systems that transmit information related to (1) light intensity and (2) spatial resolution (i.e., acuity or the ability of the eye to distinguish detail). The retinal ganglion cells of these systems have a special role concerned with processing luminance contrast (*see* later).

The rod system has a low capacity for spatial resolution but is most sensitive to light intensity. The cone system, in contrast, has a very high capacity for spatial resolution but is relatively insensitive to light; thus, it is specialized for visual acuity. The cone system also is important for color vision.

Dark and Light Adaptation

The firing frequency of a receptor and its neuronal connections declines under conditions of constant stimulation called *adaptation.* Dark adaptation to light is the adjustment to the dark that occurs during the shift from all-cone daylight vision to all-rod night vision. Rods are insensitive to longer wavelengths at the red end of the visual spectrum. Thus, a pilot flying at night, or a radiologist, can attain and retain dark-adapted vision by wearing red goggles in bright light, relying on long-wavelength red cones for visual functioning during this period.

Dark adaptation is explained by a combination of responses involving dilation of the pupils and adjustments in both the active circuitry within the retina and in the recycling of rhodopsin in the rods. The latter is critically important in the modulation of the cycle of adjustments to either increased or reduced sensitivity of the photoreceptors and the maintenance of the photoreceptive pigments. *Adaptation allows the visual system to respond effectively to the enormous range and varying degrees of luminal intensity from extremes of brightness to darkness.*

Light adaptation is associated with the retina becoming less sensitive to bright light. The phenomenon is explained by changes in the degree of pupillary constriction and the response of the photoreceptors. This response is the result of closure of the ion channels of the photoreceptors, leading to a decrease in triggering the second-messenger photoinduction cascade, thus reducing sensitivity of the receptors to light.

To summarize functional differences, the rods and cones allow the visual system to resolve the contested demands of sensitivity to light and visual acuity. The rod system is specialized for sensitivity to light at the expense of resolution for visual acuity. The cone system is specialized for visual acuity at the expense of sensitivity to light. The rods and cones both contribute to light adaptation.

The light receptors in each eye number about 91 million rods and 4.5 million cones. Within the retina, there is substantial convergence from the rods to the approximately 1 million ganglion neurons and slight to no convergence by cone systems. Within the *fovea centralis,* where visual acuity is sharpest and color vision is optimal, there is a "private-line system" of 1:1 connectivity between a cone, to a bipolar cell, to a ganglion cell, to a neuron in the lateral geniculate nucleus of the thalamus (*see* **Fig. 19.2**).

Center-Surround Receptive Fields and Center-Surround Retinal Ganglion Cells

Each of the 1 million ganglion cells in the retina receives stimulation from a spot in the environment. The cell's view of the environment is called its *center-surround receptive field.* It consists of a small circle composed of either an *on* excitatory center (like a hole in a doughnut) coupled with an antagonistic *off* inhibitory surround (the doughnut), or an *off* center and an *on* surround (*see* **Fig. 19.4**). Two classes of retinal ganglion cells are designated as either *on-center* or *off-center ganglion cells*: Each is characterized by a receptive field comprised of a center and an antagonistic surround. On-center and off-center ganglion cells are present in roughly equal numbers, with each pair of ganglion cells receiving inputs from a

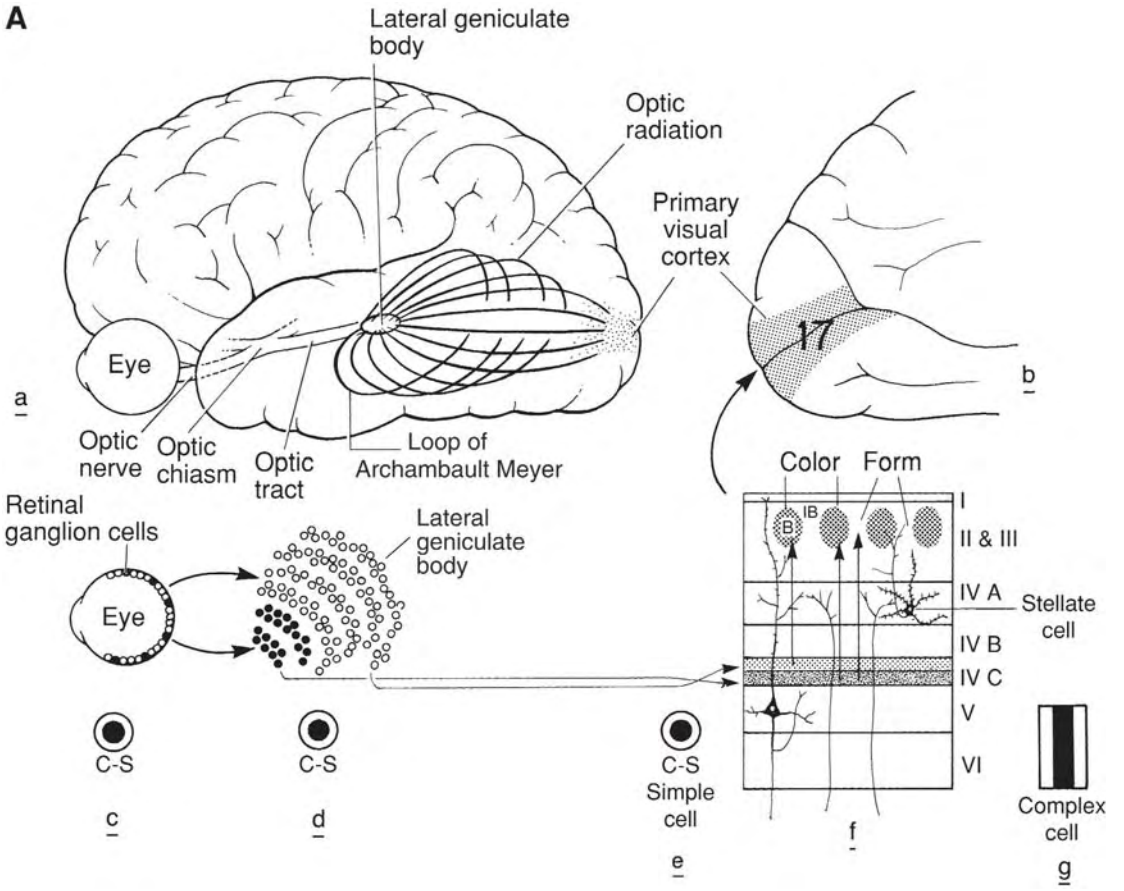


Figure 19.4: Diagram showing the functional organization of the visual system. **(A) (a)** Lateral view of visual pathway. The fibers projecting from the lateral geniculate body (LGB) to primary visual cortex (area 17, visual area 1, V1) comprise the optic radiations (geniculocalcarine pathway). **(b)** Medial view of the occipital lobe illustrating the primary visual cortex. **(c)** Ganglion cells of retina with center-surround (C-S) receptive field. **(d)** LGB: the magnocellular neurons (laminae I and II) are functionally color blind and have fast response, high-contrast sensitivity, and low resolution; parvicellular neurons (laminae III through VI) are functionally color selective and have slow response, low-contrast sensitivity, and high resolution. All neurons have center-surround receptive fields. **(e)** Cell of lamina IV (area 17) with center-surround receptive field. **(f)** Section through primary visual cortex and its laminae (see text for explanation). **(g)** Simple cell and complex cell, each with a receptive field comprised of an on-slit flanked by off-slits. **(B) (h)** Lateral view of the cerebral hemisphere showing some of Brodmann's areas and extrastriate visual areas. **(i)** Representation of portion of area 17 [refer to part **(f)**]. **(j)** Surface view of functional segregation of area 18 (visual area 2). B, blob; C-S, center-surround receptive field (on-center off-surround illustrated); IB, interblob; ITC, inferotemporal cortex; LGB, lateral geniculate body and its layers 1 through 6 (layers 1, 2, solid circles; layers 3–6, open circles); MT, middle temporal area (movement and stereopsis); STS, superior temporal sulcus; V4, visual area 4 (color). (Adapted from Livingstone and Hubel, 1988.)

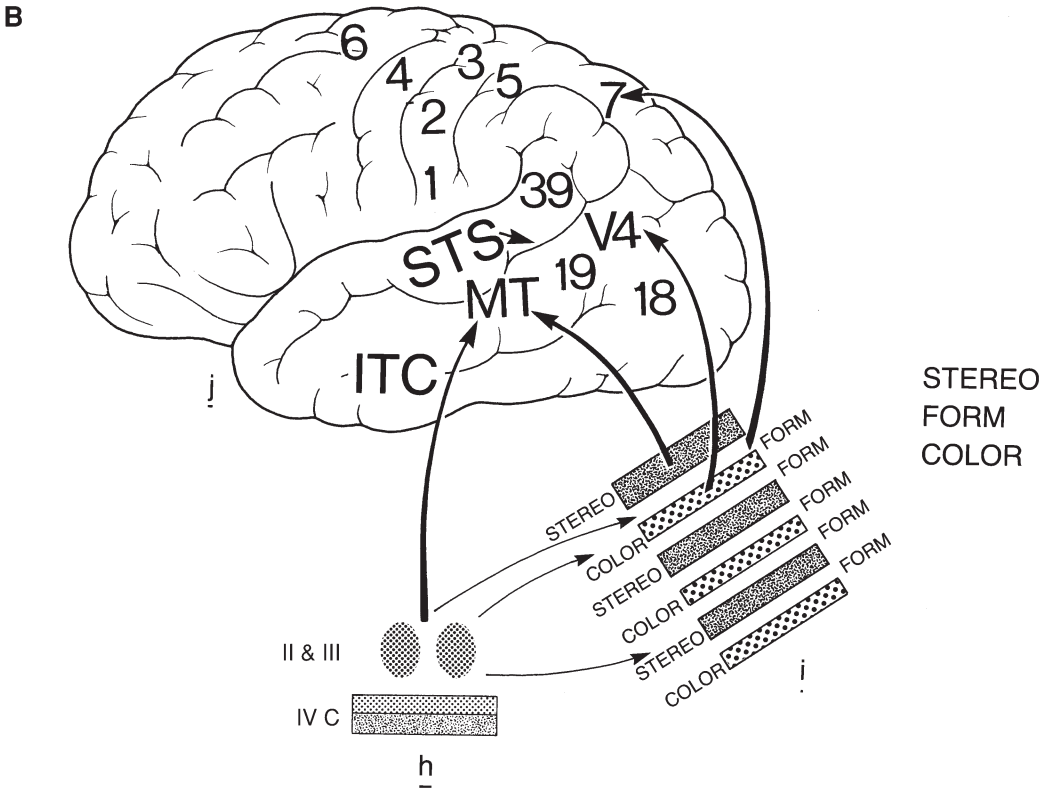


Figure 19.4 (continued)

single photoreceptor–bipolar cell sequence. In turn, each ganglion cell transmits via its axon all-or-none action potentials to a center-surround neuron in the lateral geniculate nucleus (LGN). The retinal circuitry of the bipolar cells, horizontal cells, and amacrine cells communicate via graded potentials. In contrast, the ganglion cells communicate via action potentials to the LGN. Signals from cones within the surround of a bipolar cell's receptive field are mediated by horizontal cells and the intrinsic retinal circuitry before going to the ganglion cells.

A ganglion cell is especially sensitive to luminance contrast but relatively insensitive to the overall general level of illumination; that is, the ganglion cell is responsive to the differences between the intensity level that falls on its receptive field center as contrasted to the antagonistic surround. The antagonistic organization between the center and the surround is known as *center-surround opponency.* This difference is an expression of *luminance contrast.* Actually, luminance contrast is a form of lateral inhibition (or surround inhibition, Chap. 3), which is a physiologic information processing mechanism common to all sensory systems. The essential element in this contrast process is the inhibitory dopaminergic center-surround amacrine cell that, by its inhibitory effect, enhances the intensity of the luminance contrast (Dopamine, Chap. 15).

Because of the antagonistic surround, a ganglion cell responds more vigorously to all spots of light confined to its retinal field center than to uniform illumination of the visual field. Borders and edges between light and dark (center and surround) are subjectively intensified by luminance contrast. Artists commonly take advantage of this phenomenon by darkening

the dark side of a border and whitening the light side.

Each cone in the center of a receptive center surround field synapses (1) directly with two types of bipolar cell and a horizontal cell and (2) indirectly via local retinal circuitry with amacrine cells. Each cone synapses with both on-center and off-center bipolar cells. Cones release the neurotransmitter glutamate, which inhibits (hyperpolarizes) on-center bipolar cells and excites (depolarizes) off-center bipolar cells. The bipolar cells directly synapse with retinal ganglion cells and largely determine their responses. The on-center bipolar cells, which become depolarized by the illumination of the receptive field center, depolarize (excite) an on-center ganglion cell. An off-center bipolar cell evokes the opposite response. Signals from the cones in the surround of a bipolar receptive field are conveyed by horizontal cells and the lateral retinal circuitry. The intrinsic circuitry of bipolar, horizontal, and amacrine cells leading to the retinal ganglion cells is linked by graded potentials. In turn, the ganglion cell output is transmitted centrally via action potentials.

The Roles of the Retinal Cells that Link the Photoreceptors to the Ganglion Cells

The bipolar cells provide a direct link between the photoreceptor terminals and the dendrites of both on-center and off-center ganglion cells via rod and cone pathways. The horizontal cells modulate the lateral interactions between photoreceptor terminals and the dendrites of bipolar cells and, in addition, transfer information from distant cones to bipolar cells and ganglion cells. The amacrine cells mediate (1) lateral interactions between bipolar cell terminals and the dendrites of ganglion cells and (2) antagonistic inputs from bipolar cells in the ganglion cell surround. There are over 20 different morphological types of amacrine cell that release at least 8 different transmitters. Some types have action potentials. Processing by the amacrine cells contributes to ganglion cells having different functional features. The physiological responses of the ganglion cells are largely determined by the bipolar cells and are sculpted and refined by the influences of amacrine cells.

Types of Retinal Ganglion Cells

There are a few functionally distinct categories of ganglion cell distributed throughout the retina. Those important for perception are referred to as M (<10% of the total) and P ganglion cells (80–90%), which are linked to rods and cones. They give rise to separate parallel pathways that go to the cerebral cortex. Approximately 2% of retinal ganglion cells contain an intrinsic photopigment *melanopsin* and are specialized to respond directly to luminance. They project via the optic nerve to the suprachiasmatic nucleus of the hypothalamus (retinohypothalamic tract) an integral component of the circadian cycle discussed in Chapter 21. Other ganglion cells, which in part also can be linked to melanopsin, project to subcortical centers involved in reflexes. Among these are the pretectum, part of the pupillary light reflex pathway for adjusting the size of the pupil, and the superior colliculus for coordinating head and eye movements (*see* "Control of Eye Movements").

Retinal cells designated according to size, as magnocellular (M) ganglion cells and parvocellular (P) ganglion cells are of prime significance. This correlates with the fact that the former project to the two magnocellular layers and the latter to the four parvocellular layers of the lateral geniculate nucleus (*see* **Fig. 19.4**). Both of these cell types increases in size relative to distance from the fovea, where there are only P cells. The P ganglion cells, specialized for visual acuity, are much smaller and have more restricted dendritic fields. The M cells, with wider dendritic fields, detect low luminance and movement.

Retinal ganglion cells are the recipients of highly processed information generated by the intrinsic circuitry of photoreceptors, bipolar cells, horizontal cells, and amacrine cells. The on-center and off-center ganglion cells, present in roughly equal numbers, transmit action potentials via axons of the optic nerves that partially decussate in the optic chiasm and form the optic tracts, which terminate in the LGN.

TOPOGRAPHIC (RETINOTOPIC) REPRESENTATION OF THE VISUAL FIELDS

The retina of each eye is divided into a temporal (lateral) half or *hemiretina* and a nasal (medial) half by a vertical line passing through the fovea at the posterior pole of the eye. Hemiretinas, in turn, are subdivided into upper and lower quadrants by a horizontal line through the fovea. The retina also is subdivided into three concentric circles: a small macular area, a pericentral (paramacular) area, and a peripheral (monocular) area.

Light rays that reach the eye from points in the visual fields are refracted by the cornea and the lens to form an inverted (upside down) and reversed (temporal–nasal) retinal image. In this sense, the eye resembles a camera—the retina corresponding to the film. Hence, (1) the temporal visual field is projected to the nasal hemiretina and the nasal visual field is projected to the temporal hemiretina and (2) the upper visual field is projected to the lower retina and the lower visual field is projected to the upper retina (*see* **Fig. 19.5**). Most of the visual field is shared by the two eyes (binocular field), but the monocular area (*monocular crescent*) in the extreme temporal field is seen only by the ipsilateral eye when the eyes are fixed. Images of points in the visual field are topographically formed on the retina, called a retinotopic or visuotopic representation. The retinotopic organization is present at all levels of the visual pathway. Similar to other sensory systems, the representation of different parts of the visual field is disproportionate in size throughout the pathway, reflecting the fact that the fovea has the greatest density of receptors and the peripheral retina the least, Approximately half the fibers in the optic nerve are connected with the macula.

RETINOGENICULOSTRIATE PATHWAY

The retinogeniculostriate pathway to primary visual cortex conveys elemental Information for visual perception (e.g., center surrounds) from the retina (*see* **Fig. 19.4**). The ganglion cell axons coalesce at the optic disk (blind spot) and emerge from the eyes as the optic nerves, which are surrounded by meninges. The nerves pass through the optic chiasma, where fibers from the nasal hemiretina decussate and join the fibers from the temporal hemiretina of the opposite eye, which remain uncrossed, forming the optic tract. The temporal hemiretina of one eye and the nasal hemiretina of the other eye view the same visual field so that the tract conveys information from the opposite hemifield of both eyes; that is, the optic tract on one side carries information related to the contralateral visual fields. Most fibers in the optic tract terminate in the LGN.

Lateral Geniculate Nucleus

The lateral geniculate in humans and other primates consists of six distinct cellular layers, numbered in a ventral–dorsal sequence, and separated by thin fibrous bands. Layers one and two contain larger neurons than the other four layers, dividing the LGN into magnocellular and parvocellular parts. Axons of ganglion cells project to layers 2, 3, and 5 of the ipsilateral LGN and to layers 1, 4, and 6 of the contralateral LGN (*see* **Figs. 19.4 and 19.6**). There is no crosstalk between the layers. Fibers from the lower retina terminate laterally in the lateral geniculate body (LGB), whereas fibers from the upper retina are distributed medially; macular inputs are located centrally. LGN neurons have properties that are similar to those expressed by the M and P ganglion cells, which are their source of ascending input. The LGN, like other thalamic nuclei, gets a larger descending input from the cerebral cortex, as described in Chapter 23, and also receives afferents from the brainstem reticular formation.

VISUAL CORTEX

Primary Visual (Area 17, Striate) Cortex

Primary visual cortex is located in Brodmann's area 17 largely buried within the

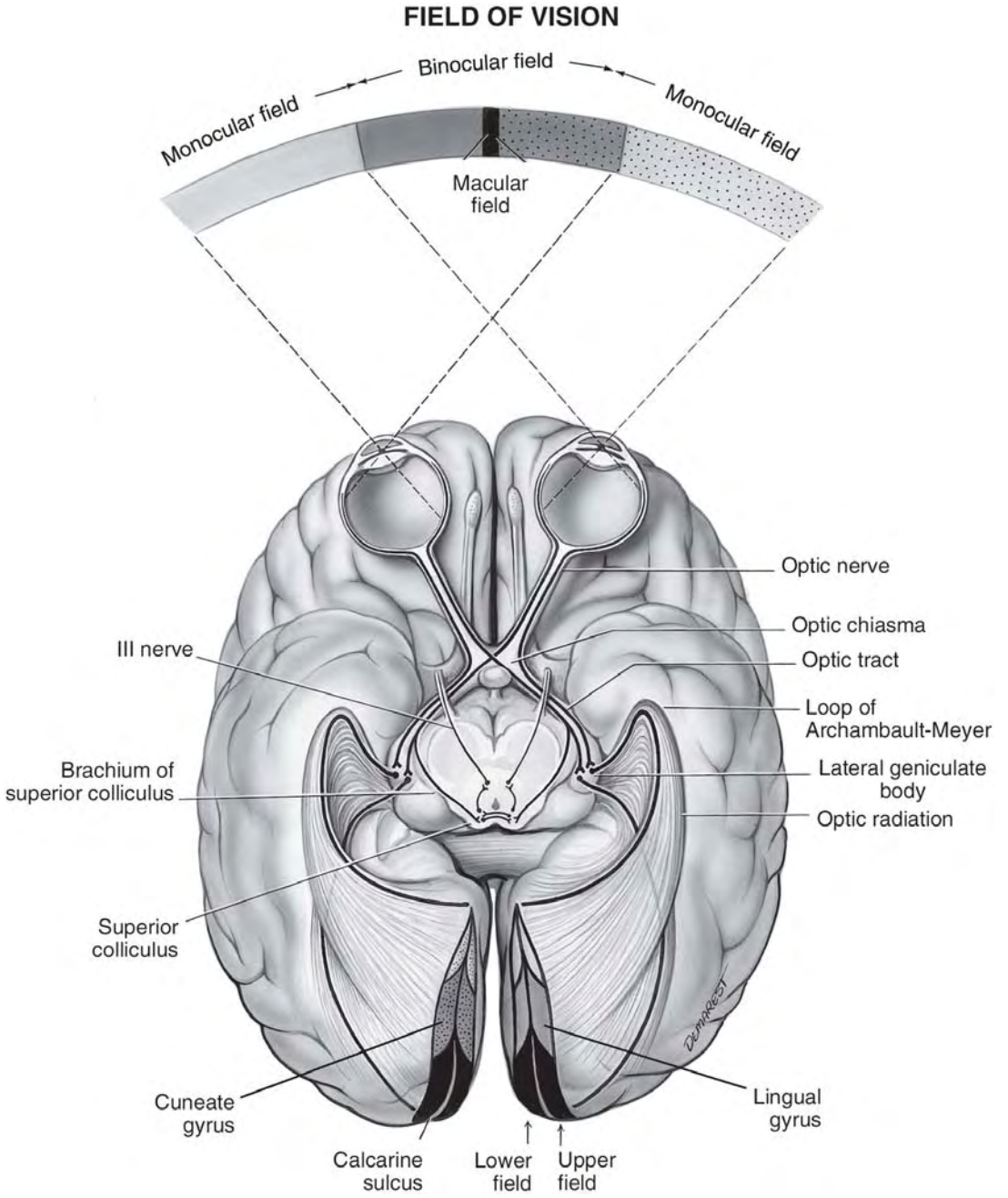


Figure 19.5: The pathway of light from visual fields to the retina to lateral geniculate bodies and to primary visual cortex. The macular field projects to the posterior aspect of primary visual cortex (solid black). The area just rostral to this receives the rest of the binocular field, and still more rostral is the area for the monocular visual field. The upper half of the visual field projects to cortex below the calcarine sulcus (lingual gyrus). The lower half of the visual field projects to cortex above the sulcus (cuneate gyrus).

calcarine fissure on the medial surface of the occipital lobe (*see* **Figs. 1.5, 1.7, and 25.3**). This cortex also is designated as the striate cortex because of a prominent band of grossly visible myelinated fibers in layer IV and as the *visual area 1 (V1)* to differentiate it from the numerous association areas numbered sequentially V2–V8. Layer IV, known as the inner granular layer because of a large concentration of small stellate cells, is highly developed and divided into IVA–IVC, which are even further subdivided.

The striate cortex is structurally laminated horizontally into six layers and functionally organized vertically into columns called *ocular dominance columns* that are about 500 μm wide and 2 mm deep (*see* **Fig. 19.6**). The ocular dominance columns are divided into *orientation preference columns,* which vary from 30 to 100 μm in width. The cells in each lamina of a column respond and share to some degree the preferences exhibited by neurons in all laminae.

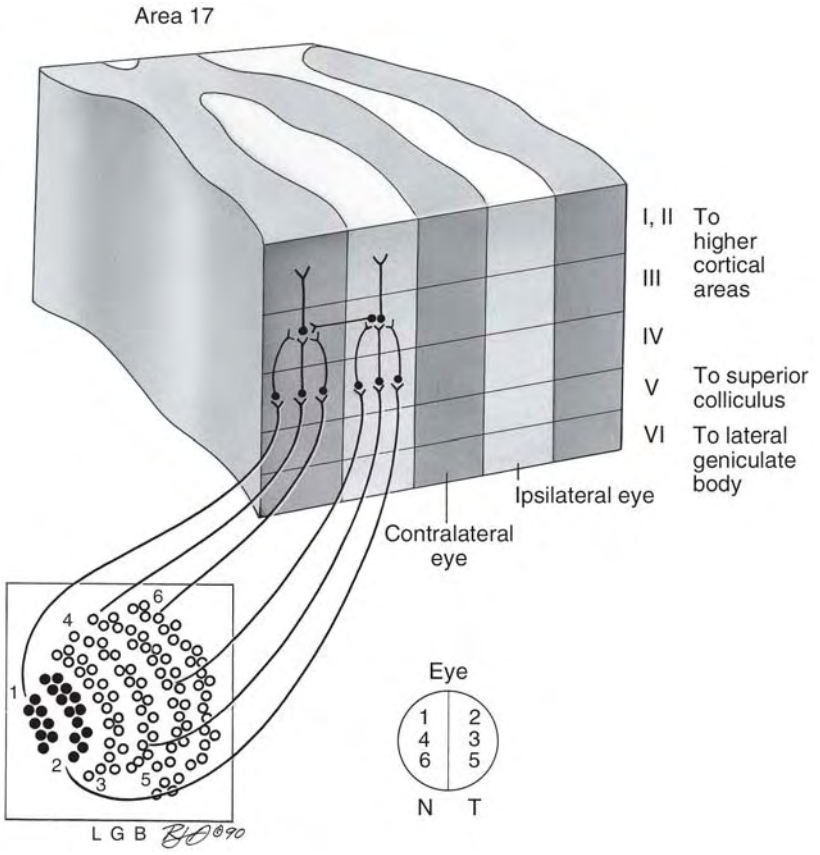


Figure 19.6: Schematic of ocular dominance columns in area 17 showing some of their connectivity. Orientation columns (not illustrated) are also present in area 17. The nasal half of the retina projects to laminae 1, 4, and 6 of the contralateral lateral geniculate body (LGB) and the temporal half of the retina to laminae 2, 3, and 5 on the ipsilateral side. The magnocellular laminae 1 and 2 are represented by solid circles and the parvocellular laminae 3–6 are represented by open circles. N, nasal half of retina; T, temporal half of retina. (Adapted from Hubel and Wiesel, 1977.)

Ocular Dominance Columns (ODC). Each cell of the lateral geniculate is strictly monocular, receiving input from one or the other eye, but not both. In turn, each LGN neuron stimulates cells in lamina IV in a column of primary visual cortex, which also contains only monocular cells. The adjacent column receives geniculocortical terminations conveying signals from the other eye. The P and M pathways remain separated—fibers from the magnocellular LGN terminate in Area 17, layer IVα and those from the parvocellular layers terminate in Area 17, layer IVβ. Cells within lamina IV interconnect with cells in more superficial and in deeper layers within the column where right and left eye columns are linked. Although neurons in these other layers of the ODC are binocular, they are dominated by the laterality of input to the lamina IV cells. Bilateral input from the two eyes through ocular dominance columns is important for depth perception of a near object and is based on the fact that the retinal images have a slightly different perspective. The functionally characterized columns are selectively responsive modules.

Orientation Preference Columns. Cortical cells that are responsive to visual stimuli mainly are classified on the basis of their receptive fields as center-surround *simple*, *complex*, or *hypercomplex.* Neurons in lamina IVC of the striate cortex are relatively unresponsive to spots of light, in contrast to the center-surround cells that characterize ganglion cells and neurons of the LGB. *S*imple cells and complex cells are responsive to short line segments with a particular orientation (vertical, horizontal, or oblique at 1 o'clock, 2 o'clock, etc.). A bar (line) of light activates a linear array of on- or off-center retinal ganglion cells and LGN neurons. The geniculocortical fibers converge on a simple cell, which is maximally excited by a line with a particular orientation. Neighboring columns have slightly different orientation preferences. An orderly shift in the axis of orientation responsiveness occurs successively in adjacent columns, which complete a 360° cycle about every 0.75 mm. *Complex and hypercomplex cells* respond optimally to edges, bars, angles, and corners and have special movement and orientation properties. These properties are explained, in part, by the convergence of inputs from simple cells. The simple and complex cells are detectors of the receptive fields of straight-line segments, whereas hypercomplex cells are detectors of curved-line segments. Area 17 has simple cells and complex cells, whereas areas 18 (V2) and 19 (V3), which also are in the occipital lobe, contain complex and hypercomplex cells. This is a step in the process that is a basis for the discrimination of form.

Blobs (Puffs) and Interblobs (Interpuffs). A regular array of zones called blobs and interblobs characterize laminae II and III of the primary visual cortex (*see* **Fig. 19.4**). The zones are defined histochemically based on whether they stain darkly and are rich in the mitochondrial enzyme cytochrome oxidase (the blobs) or stain lightly (the interblobs) (Wong-Riley et al., 1978). The blobs are color sensitive, orientation-nonspecific, and exhibit high spontaneous activity. The interblob zones are relatively color insensitive, are orientation-specific, and exhibit low spontaneous activity. Neurons in lamina I project to the other columns of the striate cortex. Neurons in laminae II–IV project to extrastriate visual areas; those in lamina V project to the superior colliculus and LGB, and those in lamina VI project back to the LGN.

In summary, the two principle roles of striate cortex are as follows: (1) To fuse the inputs from both eyes into one image. Most cortical cells of the ODCs have binocular receptive fields and have the same size, shape, and orientation and roughly the same position in the visual field of each eye. They can have a role in the perception of depth. (2) To analyze the visual world with respect to the orientation of the stimuli in the visual fields. Each image in the visual field can be decomposed into short segments of different orientation as an early step necessary for the discrimination of form.

Visual Association Areas (Extrastriate Cortex)

The multiple visual association areas are cytoarchitecturally different from primary

visual cortex. Lacking the prominent band of myelinated fibers in layer IV that characterizes area 17, they collectively are referred to as the *extrastriate cortex*. The extrastriate cortex is largely dependent on the striate cortex for functional activation. Both area 18 (V2) immediately surrounding area 17 and area 19 (V3) are in the occipital lobe (*see* **Figs. 25.5 and 25.6**). Within the extrastriate cortex, which extends into the parietal and temporal lobes, there are over 30 areas that are predominately or exclusively functionally specialized visual subareas (*see* **Fig. 19.4B**). Like V1, many have complete retinotopic maps.

THE M (MAGNOCELLULAR) AND P (PARVOCELLLAR) PATHWAYS

The processing pathways from the retina lead to the coordination of the visual field inputs from both eyes and their fusion into a single image in the striate cortex, The independent features of form, depth motion, and color (e.g., center-surround line segments) are initially demonstrated in the striate cortex. The concurrent circuitry of the M and P pathways to the striate cortex continue as parallel pathway streams to the extrastriate cortex (areas 18, 19, V2–V6, and others) for processing into congruent visual images.

The M cells and P cells (retinal ganglion cells and LGN cells) are linked together by common center-surround receptive fields, which are major components of the combined M pathway and P pathway. These two pathways project to and through primary visual cortex to the extrastriate cortex as *distributed processing streams* involved in visual perception. Within each cerebral hemisphere, (1) the dorsal or parietal stream, comprised primarily of fibers of the M stream with some contribution from the P stream, extends from the striate cortex to area 18 and through the middle temporal area (MT, V5) to the posterior parietal lobe cortex and (2) the ventral or temporal stream of combined M and P pathways extends from striate cortex to and through V2, V3, and V4 to the inferior temporal cortex (*see* **Fig. 19.4**).

The anatomic and electrophysiologic disparities between M and P ganglion cells described earlier reflect the fact that the pathways arising from the two cell types are important for different aspects of visual perception. The M cells have larger cell bodies, wider dendritic fields, and larger axon diameters. Thus, M cells have larger receptive fields and faster conduction velocities than do P cells. Magnocellular geniculate cells respond to moving stimuli and are concerned with high-sensitivity vision of form and contour, but are somewhat color-blind and lacking in resolution or fine detail. The P cells have slower conduction velocities and are less sensitive to light, but they can resolve color and fine detail. Functionally, the M cells have a more sustained response. Information about color vision is transmitted by P cells, but not by M cells. This relates to the observations that P cells are sensitive to differences in the wavelengths of light and stimulate the receptive fields of complex cells of blobs within the striate cortex. Monkeys with lesions in the magnocellular layers of the LGN do not show changes in visual acuity or perception of color, but do exhibit a reduced ability to perceive moving stimuli. In contrast, lesions of the parvocellular layers of the LGN have no effect on detection of movement, but profoundly impair visual acuity and color perception. The M pathway is especially involved with information concerning movements of objects through space. The P pathway is primarily concerned with high-resolution vision such as the detailed appreciation of the shape, size, and color of objects. The multitude of features viewed at each moment is processed in parallel by the M and P pathways and distributed to the numerous extrastriate cortical areas.

The dorsal or parietal M stream is concerned with contrast, movements of objects in space, spatial localization, and stereopsis, including where an object is. The ventral, or temporal, combination of P and M stream pathways is important for high-resolution vision, including the detailed analysis of shape, size, and color. The dorsal stream for spatial localization is channeled to the MT area and posterior parietal

lobe cortex. The ventral stream for object recognition is channeled to inferotemporal cortex. Area MT contains neurons that respond selectively to the direction of a moving edge without regard to color. Ablation of the MT in monkeys leads to impairment in the ability to perceive the direction of motion of a simulated pattern while other aspects of visual perception remain intact. In contrast, area V4 responds selectively to color without regard to direction of movement. The P stream is important for high-resolution vision—the detailed analyses of the shape size and color of objects. The ventral stream depends on both M and P systems from V1 to V4 and is divided further into two streams: one involving the striate cortex blobs for color, form, and movement and the other involving the interblobs for contrast. These differences are justification for calling the streams two parallel pathways. However, it should be noted that there is crosstalk between the two streams at the cortical level.

Details remain to be elucidated concerning the steps taken connecting the complex visual images from the patterns of dark and light that fall on the retina followed by the processing in the neuronal pathways culminating in the more abstract processing in the dorsal parietal stream and ventral inferior temporal stream of the M and P pathways to the numerous cortical visual areas. The pulvinar, which is the largest thalamic nucleus, can play a substantial role in integrating the separate pieces of information received by different regions of the extrastriate cortex. It receives its first major afferent input from the extrastriate cortex, with which it is reciprocally interconnected, and is considered to be of importance in interconnecting the visual association areas (Chap. 23).

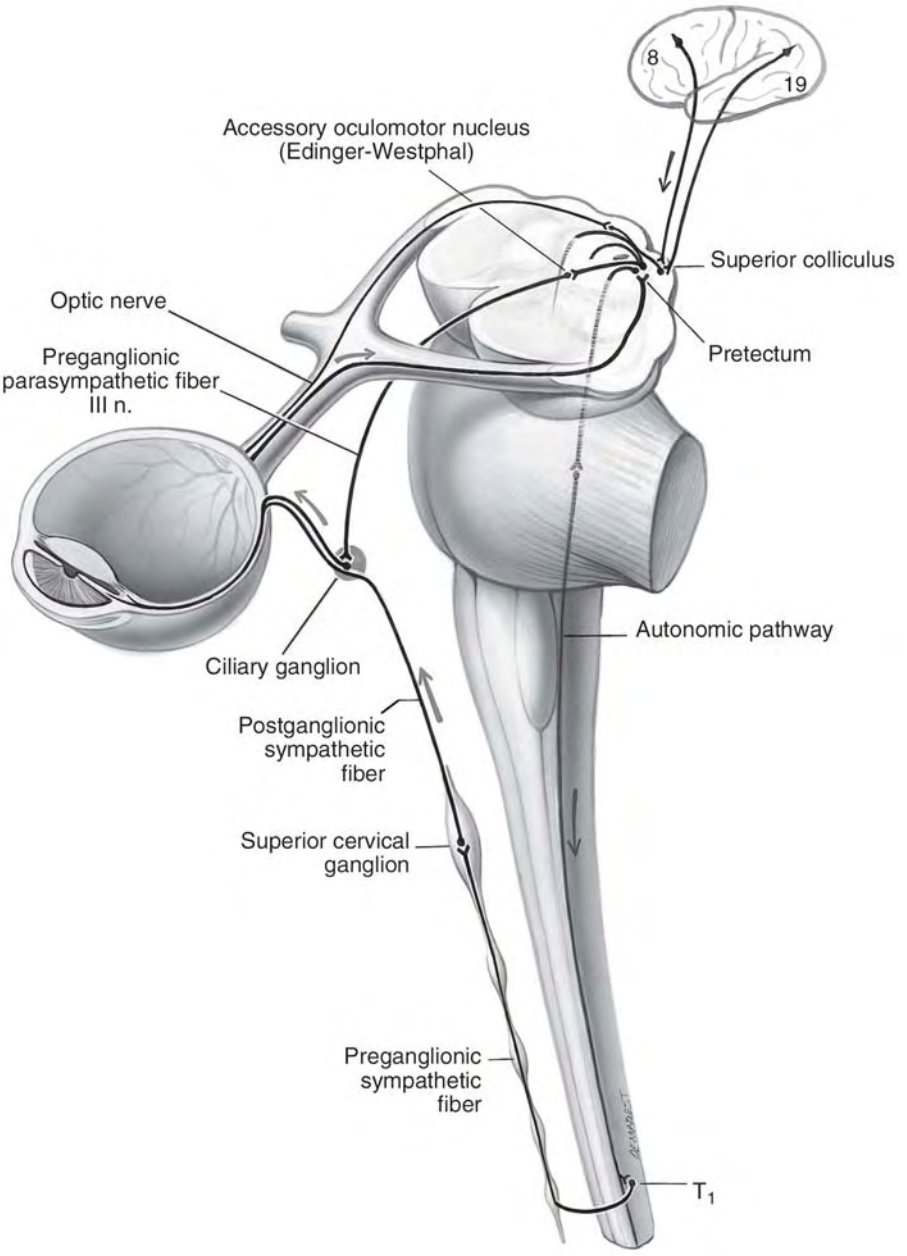
REFLEX PATHWAYS

Pupillary Light Reflex Pathway to the Pretectum (*see* Fig. 19.7)

When a bright light is directed into an eye, the pupils of both eyes constrict as a result of contraction of the constrictor muscles of the iris. The response in the stimulated eye is called the *direct light reflex* and that in the unstimulated eye is called the *consensual light reflex*. The sequence and course of neurons in this arc are as follows: Axons of the ganglion cells of each eye pass via the optic nerve, chiasma (where some of the fibers decussate), tract, and brachium of the superior colliculus before terminating bilaterally in the pretectum of the midbrain. The paired pretectal nuclei are interconnected by fibers passing through the posterior commissure. The pretectal nucleus on each side projects bilaterally to pupillomotor cells in the *accessory oculomotor nuclei of Edinger–Westphal*. The Edinger–Westphal nucleus gives rise to preganglionic parasympathetic fibers that enter the oculomotor nerve and terminate in the ciliary ganglion within the orbit. Postganglionic fibers from the ciliary ganglion elicit contraction of the constrictor smooth muscle of the iris, which decreases the diameter of the ipsilateral pupil.

The consensual light reflex occurs because the pretectum receives input from both eyes and, in turn, projects bilaterally to the Edinger–Westphal nucleus. These reflexes are carried

Figure 19.7: The pupillary light reflex and the accommodation reflex pathways and the pathway for pupillary dilatation. The light reflex pathway is mediated by axons from photopigment-containing ganglion cells that terminate bilaterally in the midbrain pretectum, located immediately in front of the superior colliculus. The pretectal nuclei are a relay to the Edinger–Westphal (E-W) nucleus on both sides. The latter gives rise to parasympathetic preganglionic fibers in the oculomotor nerve that terminate in the ciliary ganglion whose postganglionics elicit pupillary constriction. Although not classified as part of the light reflex, the diameter of the pupil is controlled by interaction between the parasympathetic and sympathetic nervous systems. The E-W nucleus also



gives rise to fibers that descend through the brainstem to the sympathetic outflow in the upper thoracic spinal cord. Preganglionics ascend to the superior cervical ganglion whose postganglionics elicit pupillary dilatation. Accommodation is mediated via (1) the ascending visual pathway, (2) descending corticocollicular fibers from the occipital (area 19), and frontal (area 8) lobes, (3) a relay in the superior colliculus to the E-W nucleus, (4) the preganglionic parasympathetic outflow through the oculomotor nerve to the ciliary ganglionic, which gives rise to (5) postganglionic fibers that activate the ciliary muscles.

out unconsciously without any cortical involvement. This reflex is preserved even after lesions involving the lateral geniculate bodies, optic radiations or visual cortex. Individuals afflicted with cortical blindness resulting from complete destruction of both striate cortices retain the light reflexes.

Accommodation Reflex Circuit (*see* Fig. 19.7)

The adjustments of the lens by the action of the ciliary body to bring an object into focus are known as accommodation. The ciliary body is the ring of tissue that encircles the lens and contains the circular and radial smooth muscle fibers that adjust the refractive power of the lens and also has a vascular component (the ciliary processes) that secretes the aqueous humor that fills the posterior and anterior chambers of the eye (*see* **Fig. 19.1**). Unlike the light reflexes, circuitry of the accommodation reflex includes the visual cortex; an individual does exert some control in selecting an object brought into focus. Impulses from the eye are relayed via the visual pathways to the visual cortex. Neurons in the visual areas have axons, which descend through the optic radiation to the superior colliculus. In turn, collicular neurons project to the preganglionic parasympathetic neurons of the accessory oculomotor nucleus of Edinger–Westphal, which, after passing through the oculomotor nerve, synapse with postganglionic parasympathetic neurons in the ciliary ganglion. These neurons innervate the smooth muscles in the ciliary body, which regulate the tension on the lens.

Accommodation–Convergence Reaction Circuit

Shifting focus from a distant object to a near one involves a triad of actions. Contraction of the ciliary muscles causes the lens to thicken in order to bring the object into focus by accommodation. The eyes converge as the medial recti muscles contract and the pupils constrict to enhance the definition of the image.

Argyll–Robertson Pupil

The Argyll–Robertson pupil can occur in syphilis of the central nervous system. In this syndrome, the pupil is small in dim light and does not constrict further when the eye is exposed to bright light. However, the same pupil will constrict further during the accommodation–convergence reaction. This syndrome is presumed to be caused by lesions in the pretectum.

Pupillary Dilatation Circuit (*see* Fig 19.7)

Descending sympathetic pathways pass through the brainstem and anterior half of the spinal cord before terminating on preganglionic neurons of the intermediolateral cell column at C8 and T1 spinal levels. The preganglionic fibers ascend through the sympathetic chain and synapse in the superior cervical ganglion. Postganglionic sympathetic axons course along branches of the internal carotid artery to reach the radial smooth muscle fibers in the iris, whose contraction dilates the pupil. Interruption of the preganglionic or postganglionic fibers results in an ipsilateral Horner's syndrome (Chap. 12); the syndrome can occur following lesions in the brainstem.

CONTROL OF EYE MOVEMENTS

The Retino–Superior–Colliculus (Retino-Tectal) Pathways for Coordinating Eye and Head Movements

The superior colliculus has a major role in coordinating eye and neck movements to detect, capture, track, and maintain the visual image on the fovea called *foveation*. The superficial layers of the superior colliculus receive direct visual input from the retina and indirect input from the visual cortex. Visual information is coordinated with auditory and vestibular inputs, which are distributed to the intermediate layers. The superior colliculus controls the proper tracking of the eyes to a vast repertoire of environmental stimuli. Superior colliculus cells are especially responsive to motion within the receptive field. Descending projections from the visual cortex and the frontal eye fields (Brodmann's area 8) project to the superior col-

liculus and to the paramedian pontine and midbrain gaze centers for control or horizontal and vertical eye movement (EOM), respectively (Chap. 16). The gaze centers provides the basis for integrated EOMs in response to sensory information that helps to locate moving objects in space. The deeper layers of the superior colliculus project to the gaze centers and are the source of the tectospinal tract for coordination of head and eye positions and tectopontine fibers for relay to the cerebellum. As with other muscle groups, the coordination of eye muscles is influenced by the cerebellum and basal ganglia (Chaps. 18 and 24).

Types of Eye Movements

Eye movements are categorized as conjugate (i.e., both eyes move in parallel) or disconjugate (i.e., eyes move in opposite directions as occurs during ocular convergence to focus on a near object). Conjugate EOMs are mediated through the superior colliculus and the paramedian pontine and midbrain reticular formation (Chap.16). Four basic types of EOMs are recognized; each is activated by an independent control system involving different regions of the brain.

1. *Fast saccadic eye movement, movement on command, searching movement*. This movement is the saccade (e.g., fast component in nystagmus), in which the eyes are searching for an object upon which to fixate. Activation of the frontal eye fields (area 8) by a "command," or stimulation of the superior colliculus, evokes this quick voluntary movement of the eyes. The visual image is suppressed during a saccade. Electrical stimulation of area 8, or of the superior colliculus, causes the eyes to deviate to the opposite side.
2. *Slow pursuit or tracking an ongoing motion*. This action occurs while following a moving object (following a bird in flight). Activation of cortical areas 18 and 19 evokes this movement.
3. *Vestibuloocular reflex (VOR) eye movements*. The VOR EOMs serve to maintain fixation of the eyes on an object while the head is in motion. It requires coordinated contraction of the extraocular muscles, which is mediated by ascending pathways of the vestibular system for control of EOMs, and by descending vestibular pathways to the neck musculature to maintain head position. This "keep eyes on target" activity is expressed as the head turns in one direction and the eyes move in the opposite direction so that the gaze remains fixed on the object.
4. *Vergence eye movements*. Influences from cortical areas 19 and 22 direct convergence so that both eyes remain fixed upon a near object. Under normal circumstances, divergence beyond the parallel position usually does not occur.

A duck hunter sitting in a gently rocking boat in a tidal marsh illustrates the action of these four systems. The hunter scans the sky for a duck using saccadic eye movements from point to point (a visual image is not recognizable during saccades because the motion during the saccade is too fast). Smooth pursuit movements follow the duck, once it is spotted. If the duck flies close by, the vergence (convergence) eye movements combine with the pursuit movements as the hunter's vision shifts from far to near vision. During the entire sequence, the hunter employs VOR movements to compensate for movements of the head caused by the rocking of the boat.

LESIONS OF THE VISUAL PATHWAYS

By convention, injury to the visual pathways causes defects described in terms of gaps in the visual field of each eye, as shown in **Fig. 19.8**. Defects limited to the same visual field of each eye are called *homonymous*, whereas those located in different fields are *heteronymous*. Partial lesions produce partial defects in the fields of vision. Damage to a small area of the retina results in a blind spot (*scotoma*) referred to the visual field of the affected eye. The *optic disk*, where the optic

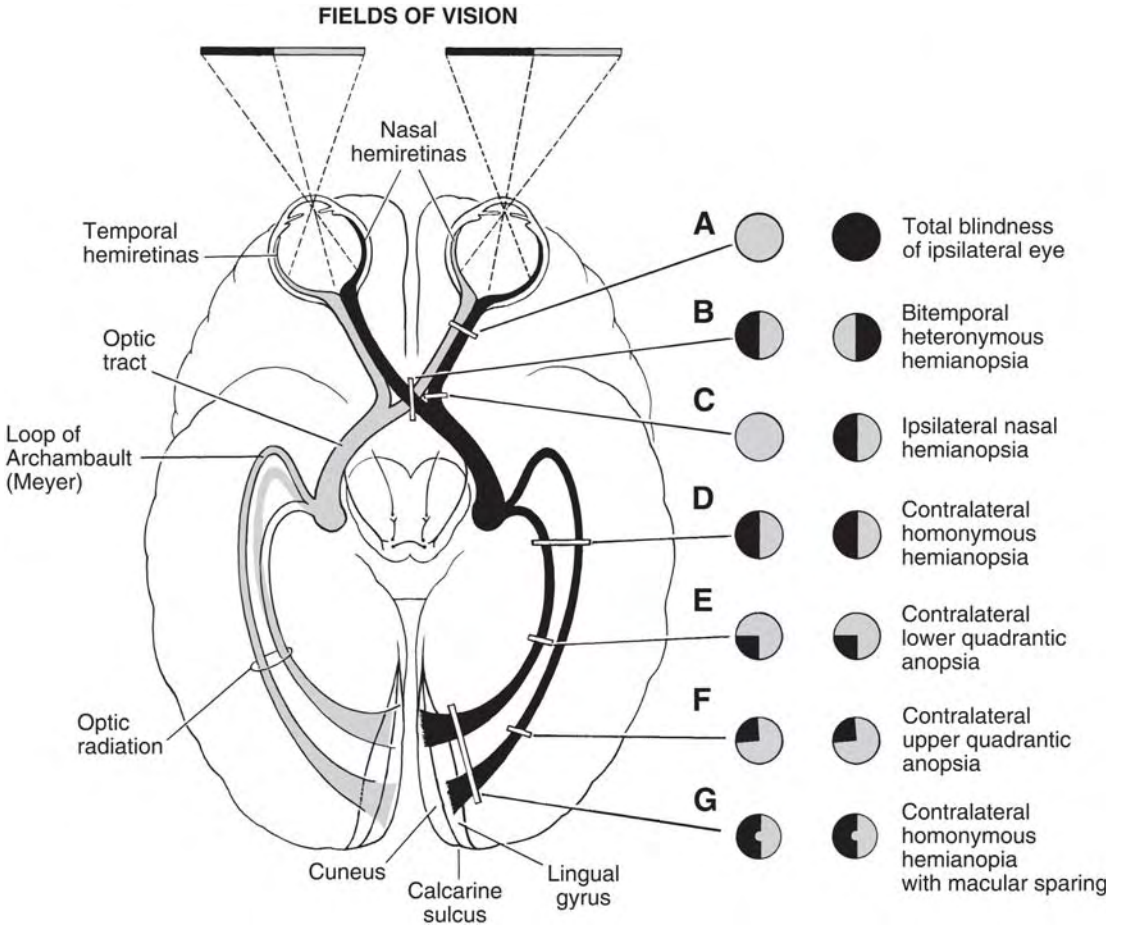


Figure 19.8: Lesions at different sites within the visual pathways. The corresponding visual field defects are represented on the right side of the drawing.

nerve fibers converge to leave the retina, is a natural blind spot because it contains no receptors. The optic disk is 3 mm (15() medial to the fovea. Thus, because of reversal of the image, the blind spot is 15° lateral (i.e., in the temporal field). Complete interruption of the optic nerve results in permanent blindness in one eye (*see* **Fig. 19.8A**). The direct light reflex in that eye is eliminated. However, a blind eye can still accommodate and exhibit the consensual light reflex because the normal eye activates the intact efferent part of the reflex arc to the blind eye. On the other hand, the consensual light reflex is eliminated in the normal eye because the afferent limb of the reflex from the blind eye is interrupted.

A *midline lesion of the optic chiasma* (following compression from a tumor of the pituitary gland or from a craniopharyngioma located immediately behind the chiasma) can interrupt the decussating fibers from both eyes (*see* **Fig. 19.8B**). This results in blindness in the nasal half of the retina (the temporal half of the visual field of each eye); it is called *bitemporal heteronymous hemianopsia* (*hemianopia*) or tunnel vision. Damage to the nondecussating fibers on one (right) side of the optic chiasma results in a *right nasal hemianopsia* (*see* **Fig.**

19.8C) (i.e., blindness in the temporal half of the retina [nasal half of the visual field of one eye]). The complete interruption of the optic tract, lateral geniculate body, optic radiations, or the entire primary visual cortex on one side (e.g., right) results in a *contralateral homonymous hemianopsia*, or blindness in the field of vision on the side opposite (left) the lesion (*see* **Fig. 19.8D**). *Macular sparing* (preservation of the visual field of the maculae) sometimes occurs following strokes involving the visual cortex. This phenomenon is attributable to a dual vascular supply to this region from branches of both the middle and posterior cerebral arteries as well as to the extensive cortical representation of the central visual field. A lesion of the entire cuneate gyrus (includes entire primary visual cortex above the calcarine sulcus) on one side results in *contralateral homonymous lower quadrantic anopsia* (*see* **Fig. 19.9E**) because pathways from the upper temporal quadrant of the ipsilateral retina and upper nasal quadrant of the contralateral retina are interrupted. Conversely, a lesion of the lingual gyrus (below the calcarine sulcus) or interruption of the optic radiations on one side as they pass through the temporal lobe (loop of Archambault–Meyer) results in *contralateral homonymous upper quadrantic anopsia* (*see* **Fig. 19.8F**) because pathways from the lower temporal quadrant of the ipsilateral retina and lower nasal quadrant of the contralateral retina are interrupted.

A lesion in cortical area 8 in one hemisphere results in the deviation of the eyes to the same side.

SUGGESTED READINGS

Adams DL, Zeki S. Functional organization of macaque V3 for stereoscopic depth. *J. Neurophysiol.* 2001;86:2195–2203.

Adams MM, Hof PR, Gattass R, Webster MJ, Ungerleider LG. Visual cortical projections and chemoarchitecture of macaque monkey pulvinar. *J. Comp. Neurol.* 2000;419:377–393.

Dacey DM. Parallel pathways for spectral coding in primate retina. *Annu. Rev. Neurosci.* 2000;23: 743–775.

Dacey DM, Packer OS. Colour coding in the primate retina: diverse cell types and cone-specific circuitry. *Curr. Opin. Neurobiol.* 2003;13: 421–427.

Dacey DM, Peterson BB, Robinson FR, Gamlin PD. Fireworks in the primate retina: in vitro photodynamics reveals diverse LGN-projecting ganglion cell types. *Neuron* 2003;37:15–27.

Desimone R. Neural mechanisms for visual memory and their role in attention. *Proc. Natl. Acad. Sci. USA* 1996;93:13494–13499.

Deyoe EA, Trusk TC, Wong-Riley MT. Activity correlates of cytochrome oxidase-defined compartments in granular and supragranular layers of primary visual cortex of the macaque monkey. *Vis. Neurosci.* 1995;12:629–639.

Dowling JE. *The Retina: An Approachable Part of the Brain.* Cambridge, MA: Belknap Press of Harvard University Press; 1987.

Grill-Specton K, Levan AC. The human visual cortex. *Ann. Rev. Neurosci.* 2004;27:649–677.

Hattar S, Liao HW, Takao M, Berson DM, Yau KW. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science* 2002;295:1065–1070.

Hattar S, Lucas RJ, Mrosovsky N, et al. Melanopsin and rod-cone photoreceptive systems account for all major accessory visual functions in mice. *Nature* 2003;424:75–81.

Hubel DH. *Eye, Brain, and Vision.* New York: Scientific American Library; 1987.

Hubel DH, Wiesel TN. Functional architecture of macaque monkey visual cortex. *Proc. R. Soc. Lond. B: Biol. Sci.* 1977;198:1–59.

Kleinschmidt A, Buchel C, Zeki S, Frackowiak RS. Human brain activity during spontaneously reversing perception of ambiguous figures. *Proc. R. Soc. Lond. B: Biol. Sci.* 1998;265:2427–2433.

Livingstone M, Hubel D. Segregation of form, color, movement, and depth: anatomy, physiology, and perception. *Science* 1988;240:740–749.

Marcus DS, Van Essen DC. Scene segmentation and attention in primate cortical areas V1 and V2. *J. Neurophysiol.* 2002;88:2648–2658.

Oyster CW. *The Human Eye: Structure and Function.* Sunderland MA: Sinauer Associates; 1999.

Purves D and Lotto RB. *Why We See What We Do: An Empirical Theory of Vision.* Sunderland, MA: Sinauer Associates; 2003.

Rodieck RW. *The First Steps in Seeing.* Sunderland MA: Sinauer Associates; 1998.

Shipp S, Zeki S. The functional organization of area V2, II: the impact of stripes on visual topography. *Vis. Neurosci.* 2002;19:211–231.

Van Essen DC, Lewis JW, Drury HA, et al. Mapping visual cortex in monkeys and humans using surface-based atlases. *Vis. Res.* 2001;41: 1359–1378.

Wong-Riley MT, Hevner RF, Cutlan R, et al. Cytochrome oxidase in the human visual cortex: distribution in the developing and the adult brain. *Vis. Neurosci.* 1993;10:41–58.

Wong-Riley M, Antuono P, Ho KC, et al. Cytochrome oxidase in Alzheimer's disease: biochemical, histochemical, and immunohistochemical analyses of the visual and other systems. *Vis. Res.*1997;37:3593–3608.

Zeki S. *A Vision of the Brain.* Oxford: Blackwell Scientific; 1993.

Zeki S. Improbable areas in the visual brain. *Trends Neurosci.* 2003;26:23–26.

20
Autonomic Nervous System

The Somatic Motor and Autonomic Nervous Systems Compared
General Organization of the Autonomic Nervous System
Sympathetic (Thoracolumbar) Division
Parasympathetic (Craniosacral) Division
Enteric (Gut) Division ("Gut-Brain," "Minibrain")
Sensory and Humoral Systems
Central Autonomic Control Circuits
Denervation Sensitivity and Sympathectomy
Neural Control of the Urinary Bladder
Megacolon (Hirschsprung) Disease

The contraction (or relaxation) of muscles and the secretion of glands is an overt expression of the functional activity of the nervous system. These actions are mediated through the somatic motor system and the autonomic (visceral) nervous system. The *somatic motor system* innervates the voluntary (skeletal, striated) muscles, whereas the *autonomic nervous system* influences the activities of involuntary (smooth) muscles, cardiac (heart) muscle, and glands. The autonomic nervous system is often called the *general visceral efferent system* or *vegetative motor system* because the effectors are associated with the visceral systems over which only minimal, if any, direct conscious control can be exerted.

THE SOMATIC MOTOR AND AUTONOMIC NERVOUS SYSTEMS COMPARED

The role of the somatic motor system is to regulate and perform the coordinated muscular activities associated with the maintenance of posture and with phasic movements; these expressions are related to adjustments to the external environment. The general role of the autonomic nervous system (ANS) is to influence those visceral activities that are directed toward maintaining a relatively stable internal environment. For example, functional expressions of the activity of the ANS are the maintenance of (1) blood pressure commensurate with the demands of the organism and (2) a constant body temperature. These two systems are not independent; they interact. With a drop in body temperature, the somatic motor system responds by generating heat through contraction of voluntary muscles, and the ANS simultaneously stimulates the constriction of cutaneous blood vessels to reduce radiational heat loss. In general, the somatic system reacts rapidly to stimulation, whereas the autonomic system responds with a greater lag time.

The two systems differ significantly with reference to the anatomic organization of the final neuronal linkage between the central nervous system (CNS) and the peripherally located effectors. The somatic motor system has a *one-neuron linkage* to alpha and/or gamma motoneurons. From a cell body in the brainstem or spinal cord, each somatic LMN gives rise to an axon that passes through a cranial or spinal nerve to make synaptic connections with voluntary muscle fibers (Chap. 11).

In contrast, the autonomic system has a *two-neuron linkage* to peripheral effectors (*see* **Fig. 20.1**). The first neuron, called a *preganglionic neuron*, originates in the brainstem or spinal cord and has an axon that passes through a cranial or peripheral nerve and synapses, either directly or via an interneuron, with a second neuron (or neurons) located in an *autonomic ganglion* outside the CNS, This second neuron, called a *postganglionic neuron*, or autonomic

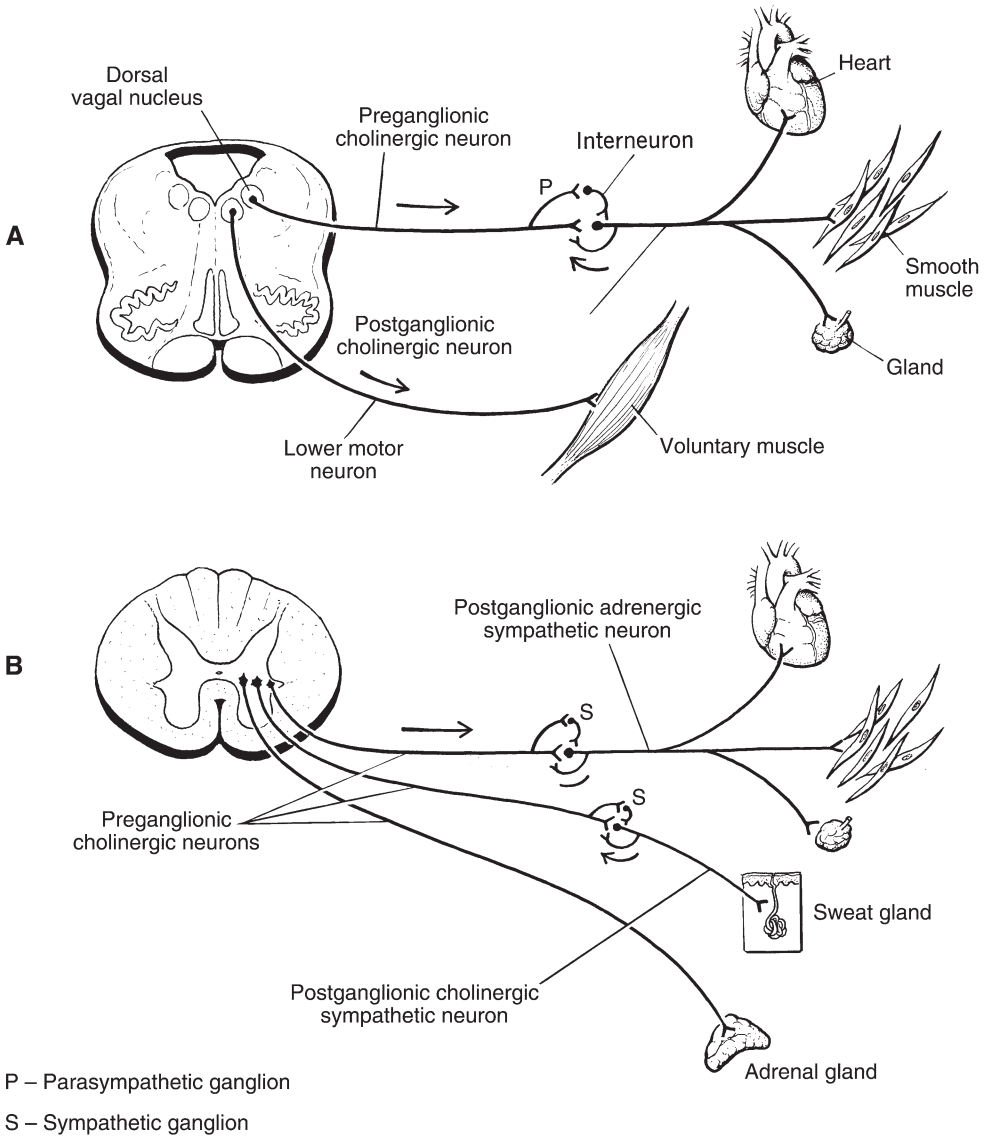


Figure 20.1: Motor innervation of the peripheral effectors. **(A)** The parasympathetic outflow from the medulla innervates cardiac muscle, smooth muscle, and glands. The lower motoneuron innervates striated muscle. **(B)** Sympathetic outflow from the spinal cord innervates cardiac muscle, smooth muscle, and glands. Sympathetic ganglia have interneurons called small intensely fluorescent (SIF) cells, which contain catecholamine fluorescent dopamine and norepinephrine.

motoneuron, has an axon that terminates in endings associated with smooth muscles, cardiac muscle, or glands and, as recently recognized, cell constituents associated with immune organs. The preganglionics are myelinated B fibers and the postganglionics are unmyelinated C fibers. When denervated, smooth muscles and glands generally continue to show significant levels of activity.

Although the ANS frequently is considered only in terms of its preganglionic and postganglionic motor components, there are extensive ascending and descending visceral pathways, just as in the somatic system.

GENERAL ORGANIZATION OF THE AUTONOMIC NERVOUS SYSTEM

The ANS is composed of three divisions or systems: (1) sympathetic (*see* **Fig. 20.2**), (2) parasympathetic (*see* **Fig. 20.3**), and (3) enteric (*see* **Fig. 20.4**).

The *sympathetic division* stimulates those activities that are mobilized by the organism during emergency and stress situations, the so-called "fight, fright, and flight" responses. These include acceleration of the rate and force of the heartbeat, increase in the concentration of blood sugar, and increase in blood pressure. In contrast, the *parasympathetic system* stimulates activities associated with conservation and restoration of body resources. These include a decrease in heart rate and a rise in gastrointestinal activities associated with increased digestion and absorption of food. The enteric nervous system (ENS) is involved in gut functioning and can operate without CNS control.

The sympathetic division is also called the *thoracolumbar* or *adrenergic system* because (1) its preganglionic fibers emerge from all thoracic and the upper two lumbar levels (T1 through L2) and (2) the neurosecretory transmitter released by the postganglionic fibers in most loci is norepinephrine, also known as noradrenalin.

The parasympathetic division is also called the *craniosacral* or *cholinergic system* because (1) its preganglionic fibers emerge with cranial nerves III, VII, IX, X and at spinal cord levels S2–S4 and (2) the neurosecretory transmitter released by the postganglionic fibers is acetylcholine.

The *enteric division* (ENS), also called the *gut brain* or *minibrain*, is an intrinsic network of neurons and connections that extends along the entire length of the digestive system (*Gr.* enteron) from the esophagus to the rectum, otherwise known as the enteron gut or gastrointestinal (GI) tract. Two interconnected ganglionic plexuses form the ENS. Sensory neurons communicate via interneurons with the two plexuses: Auerbach's myenteric plexus and Meissner's submucosal plexus (*see* **Fig. 20.4**). (1) The motor Auerbach's myenteric plexus, consisting of radially oriented axons, is located between the circular and longitudinal smooth muscle laminae of the external muscularis layer. It controls gut motility. The enteric sensory neurons are integrated into enteric feedback circuits projecting centripetally to the abdominal prevertebral, celiac, and superior and inferior mesenteric ganglia adjacent to the posterior abdominal wall; these ganglia project back to the gut. (2) Meissner's plexus, located in the submucosa of the gut, is concerned with chemical monitoring of gut contents and controlling glandular secretion. A key feature of the ENS is its anatomical and physiological independence. With this system intact, the gut can function autonomously even when completely deprived of sympathetic and parasympathetic innervation. *Functionally, the submucosal plexus controls the secretory functions of the gut and the myenteric plexus controls gut motility.*

SYMPATHETIC (THORACOLUMBAR) DIVISION

The organization of the sympathetic system is illustrated in **Fig. 20.2**. The peripheral and central control of each target organ comes from preganglionic neurons in a continuum of spinal cord segments with functionally differentiated

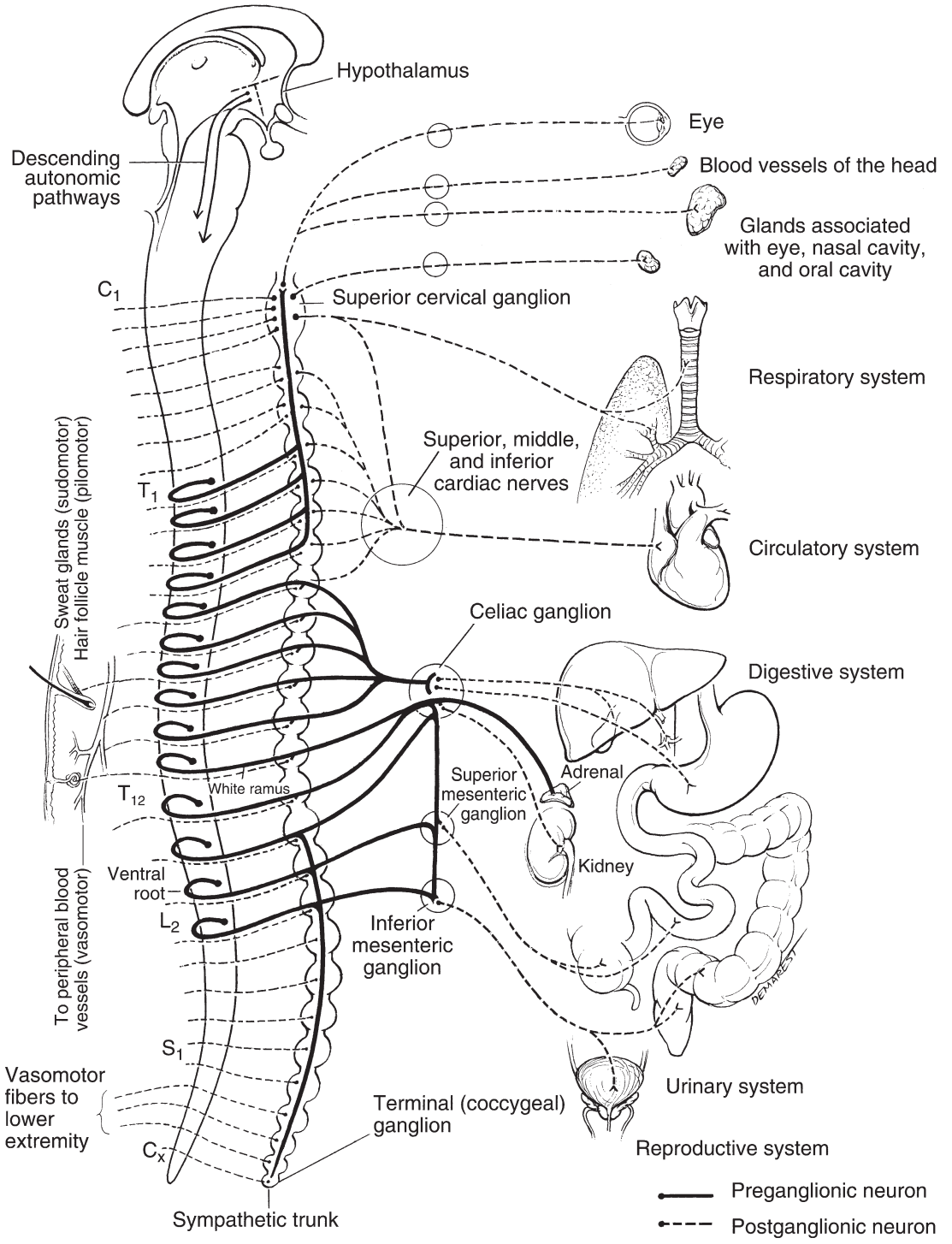


Figure 20.2: The sympathetic (thoracolumbar) division of the autonomic nervous system.

columns of neurons. *Preganglionic fibers of the sympathetic system originate from cell bodies located in the intermediolateral nuclei of lamina VII, which extends from spinal levels T1 through L2.* Visceral afferents to the sympathetic preganglionic neurons are conveyed via fibers of the dorsal roots to the spinal cord and by cranial nerves via relays in the solitary nucleus, as noted in Chapters 7 and 14. The preganglionic sympathetic fibers pass successively through the ventral roots (referred to as the *thoracolumbar outflow*), spinal nerves, white rami communicantes (branches of the spinal nerves) and the sympathetic trunk (*see* **Fig. 7.2**). The fibers terminate in either (1) paravertebral ganglia of the sympathetic chain (trunk) or (2) they pass through the chain and enter visceral nerves, which go to prevertebral (collateral) ganglia (*see* **Fig. 20.2**). The paravertebral ganglia, which are located along the bodies of the vertebral column from upper cervical through coccygeal levels, receive their input exclusively from the thoracolumbar sympathetic outflow. The paired sympathetic chains meet in the midline in a terminal ganglion on the coccyx, called the *ganglion impar* or *coccygeal ganglion*. The prevertebral ganglia are located in the abdomen adjacent to the abdominal aorta and its main branches: the celiac, aorticorenal, and superior mesenteric and inferior mesenteric ganglia (derived from T6 through L2 spinal levels). The sympathetic ganglia contain small intensely fluorescent (SIF) inhibitory interneurons (*see* **Fig. 20.1**) that mainly are dopaminergic.

Paravertebral ganglia project to the viscera of all somatic dermatomes (*see* **Fig. 20.2**). Postganglionic fibers from cells in the paravertebral ganglia pass via the gray rami communicantes (1) and spinal nerves before terminating in the sweat glands and smooth muscles of blood vessels and hair (erector pili muscles) of the body wall and extremities and (2) small nerves and perivascular plexuses to the visceral structures of the head and thorax (e.g., pupillary dilator muscle, heart, and bronchioles). Axons from the superior cervical ganglia follow the internal carotid artery before joining nerves that target cranial viscera, including in the eye and pineal gland. Vasoconstrictor, pilomotor, sudomotor, and secretomotor neurons are included. Stellate ganglia at the rostral end of the sympathetic chain emit postganglionic fibers to the heart, lungs, neck, and upper extremities. The paravertebral ganglia do not project to the extremities along the major blood vessels. Splanchnic nerve projections to the viscera mainly innervate blood vessels. The prevertebral ganglia, which regulate motility and secretions, receive input from midthoracic and upper lumbar spinal cord segments. Postganglionic fibers arising from the prevertebral ganglia form perivascular plexuses innervating the abdominal and pelvic viscera.

Diffuse and extensive branching patterns are characteristic of postganglionic noradrenergic nerves of the sympathetic nervous system. A single neuron can have many terminal branches over 14 cm long with several thousand varicosities containing the transmitter (norepinephrine) and modulators (Neuropeptides, Chap. 15). These varicosities make numerous *en passage "synaptic junctions"* with muscle and glandular cells (*see* **Fig. 15.4**). The visceral effector is a muscle bundle rather than a single cell; individual muscle cells are linked and coupled by gap junctions, which cause electrotonic spread of activity between them.

In general, the sympathetic outflow is distributed as follows: T1–T5 to the head and neck, T1–T2 to the eye, T2–T6 to the heart and lungs, T6–L2 to the abdominal viscera, and L1–L2 to the urinary, genital, and lower digestive systems.

The *neurotransmitter* released by the preganglionic nerve terminals is *acetylcholine*, which is deactivated rapidly by *cholinesterase or recycled*; that released by the postganglionic nerve terminals is *norepinephrine (noradrenalin, levarterenol)* and is either deactivated slowly by *monoamine oxidase (MAO)* and *catechol-O-methyl transferase (COMT)* or retrieved by reuptake for reuse by the nerve terminals (Chap.15). The MAO is located intracellularly, whereas COMT is extracellular.

Adrenal Gland

The cells of the medulla of the adrenal gland are actually specialized postganglionic neurons. Preganglionic cholinergic fibers from T6 to T9 stimulate the adrenal chromaffin cells to release both epinephrine and norepinephrine into the circulatory system, which distributes these neurosecretions through the body. Within the medulla, there are about eight cells that release epinephrine to one cell that releases norepinephrine. The adrenal medulla-released transmitters act in conjunction with the norepinephrine released by sympathetic postganglionic fibers. In humans and other mammals, where the adrenal cortex and medulla are juxtaposed, epinephrine is the main catecholamine. The adrenal cortex envelops the medulla and synthesizes glucocorticoids, which are essential for the conversion of norepinephrine to epinephrine.

Systemic Effects of Sympathetic Innervation

The sympathetic system is structurally and functionally organized to exert its influences over widespread body regions or even the entire body for sustained periods of time. Every preganglionic neuron has a relatively short axon, which synapses with many postganglionic neurons, each of which has a long branching axon forming numerous neuroeffector junctions over a wide area. The widespread and sustained sympathetic effects are the result of the slow deactivation of norepinephrine and of the systemic distribution of norepinephrine and epinephrine released by the adrenal medulla.

PARASYMPATHETIC (CRANIOSACRAL) DIVISION

The cranial portion of the parasympathetic system is associated with four cranial nerves (III, VII, IX, and X) that supply innervation to the head, thorax, and most of the abdominal viscera (*see* **Fig. 20.3**). The sacral portion takes origin from spinal cord levels S2–S4 and supplies innervation to the lower abdominal and pelvic viscera. The body wall and the extremities do not have a parasympathetic innervation.

Following is a list of the four cranial nerve brainstem preganglionic parasympathetic nuclei, their connections, and the organs innervated (*see* **Fig. 20.3**). (1) Preganglionic fibers from the accessory oculomotor nucleus of Edinger–Westphal in the midbrain pass via the oculomotor nerve and terminate in the ciliary ganglion. Postganglionic neurons innervate the sphincter (constrictor) muscles of the pupil and the ciliary muscles involved with accommodation (focusing the lens of eye). (2) Preganglionic fibers from the superior salivatory nucleus pass via cranial nerve VII and terminate in the pterygopalatine and submandibular ganglia. Postganglionic neurons innervate numerous glands in the head, including lacrimal, submandibular, and sublingual glands and glands of the nasal, oral, and pharyngeal cavities. (3) Preganglionic fibers from the inferior salivatory nucleus pass via the glossopharyngeal nerve and terminate in the otic ganglion on postganglionic neurons that innervate the parotid gland. (4) Preganglionic fibers from the dorsal motor nucleus of the vagus pass via cranial nerve X and synapse in terminal ganglia (located adjacent to or within visceral organs). Postganglionic neurons innervate the viscera of the thorax and abdomen (e.g., heart, lungs, and GI tract) as far as the splenic flexure (junction of transverse and descending colon on left side). The vagus nerve is prototypical of the parasympathetic system. Its long preganglionic axons synapse in terminal ganglia located in or near the targets of the very short postganglionic axons with little divergence. Hence, the effects are localized rather than widespread. It is interesting to note that of the 5000 neurons of the vagus nerve innervating the gut, about 90% are afferent neurons and only 10% are preganglionic parasympathetic neurons.

The pelvic hypogastric plexuses comprise the ganglia controlling the genitourinary organ systems. The sacral portion of the parasympathetic system originates from cell bodies mainly in the gray matter of levels S2–S4; the preganglionic neurons pass via the pelvic

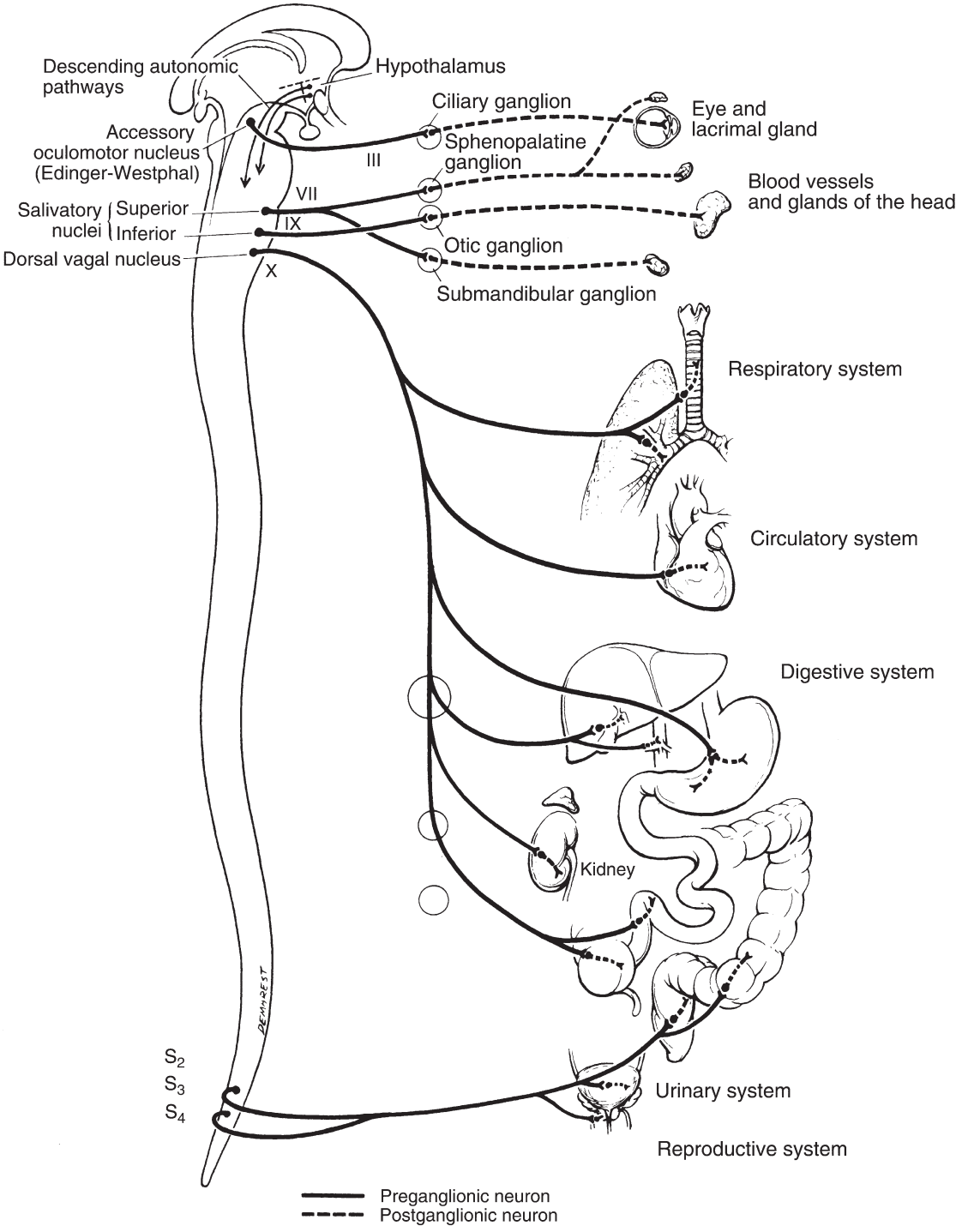


Figure 20.3: The parasympathetic (craniosacral) division of the ANS.

splanchnic nerves to synapse in terminal ganglia whose postganglionic neurons innervate the lower abdominal and pelvic viscera comprising the colon distal to the left colic flexure and the urogenital viscera. The sacral parasympathetic outflow is involved with the "mechanisms of emptying" by urination and defecation and with erection.

With regard to the urinary bladder, the norepinephrinergic sympathetic innervation contributes to the relaxation of the detrusor muscle (muscle of the bladder) and increased tone of the internal sphincter. The cholinergic parasympathetic innervation stimulates contraction of the detrusor muscle and relaxation of the internal sphincter.

With regard to the pelvic GI tract, the sympathetic innervation contributes to decreased motility of the sigmoid colon and rectum and contractions of the internal sphincter. The parasympathetic innervation stimulates increased motility of the sigmoid colon and rectum and decreased tone of the internal sphincter.

Except for the voluntary striated muscles of the external sphincter innervated by somatic motor nerves, the musculature of the pelvic viscera consists of smooth involuntary musculature innervated by the ANS.

The pararsympathetic system is primarily organized to respond transiently to a specific stimulus in localized and discrete regions. Each long preganglionic axon synapses with a few postganglionic neurons with short axons, exerting influences over a small area. The rapid deactivation of acetylcholine by cholinesterase restricts the time course over which a specific quantity of released acetylcholine is effective.

ENTERIC DIVISION ("GUT-BRAIN," "MINIBRAIN")

The organization of the enteric system is illustrated in **Fig. 20.4**. The enteric system, conceptualized as the "brain of the gut", carries out automatic functions. It contains approximately 100 million neurons, about the same number as in the entire spinal cord. About 10 different cell types have been described releasing more than 20 different transmitters and modulators. Enteric ganglia form an intrinsic nervous system, processing peripheral and centrally integrated information and coordinating the activity of all component parts of the gut. They regulate digestive processes by exerting local reflex control over parasympathetic outflows to the gut. The ENS controls the functions of the GI tract, pancreas, and gallbladder. The ENS has a complex neural organization. It promotes homeostasis by regulating gut blood vessel tone, motility, fluid transport, nutrient absorption, and enterochromaffin cell glandular activity (*see* "The Peristaltic Reflex"). The network is comprised of sympathetic and parasympathetic preganglionic neurons and parasympathetic postganglionic neurons, in addition to local sensory neurons and interneurons (*see* **Fig. 20.4**). It is responsive to alterations in the tension of the gut wall and to changes in the chemical environment within the gut. The enteric motor neurons control the smooth muscle of the gut and local blood vessels, as well as secretions of the glandular cells of the mucosa.

In essence, neurons of the ENS are organized as a mini nervous system that consists of two major plexuses of neurons that extend as continuums along the entire length of the GI tract. These are (1) the myenteric plexus (Auerbach's plexus) located between the inner circular and outer longitudinal smooth muscle layers of the muscularis externa and (2) the submucosal plexus (Meissner's plexus) located in the submucosa, with branches extending into the mucosa. In general, Auerbach's plexus controls motility of the gut (peristalsis) and Meissner's plexus is involved with the secretory aspects of gut function.

The parasympathetic postganglionic neurons receive neural influences from (1) intrinsic sensory neurons and interneurons within the gut and (2) the extrinsic preganglionic parasympathetic neurons and postganglionic sympathetic fibers. The *intrinsic sensory neurons* with cell bodies located in the submucosa and external muscular layer of the gut have dendritic processes that

extend into the mucosal layer. Dendritic processes of the mechanosensory and chemosensory cells respond to tension (stretch) within the gut proper, tonicity, and the chemical environment within the gut lumen. Sensory afferent neurons respond to mediators released from the several types of enteroendocrine cell of the mucosal epithelium (*see* "The Enteroendocrine System"). They have been likened to enteric taste buds, which transduce signals generated by

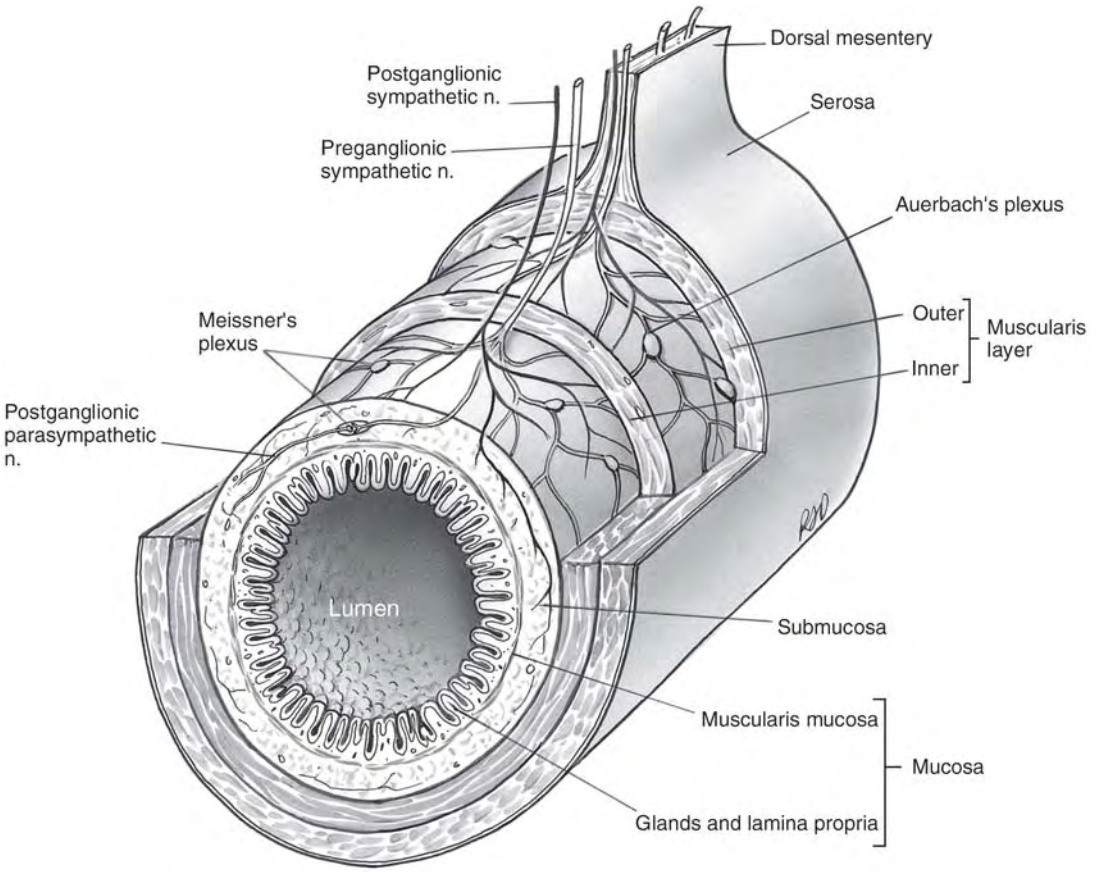


Figure 20.4: The enteric division of the ANS. Schema of the sympathetic and parasympathetic innervation of the gastrointestinal (GI) tract. The general visceral efferent (GVE) innervation of the smooth muscles and glands of the small intestine by the sympathetic (dark black line) and parasympathetic (light double lines) nervous systems. From their location between the two peritoneal layers of the dorsal mesentery the nerve fibers of these systems enter and are distributed as the components of (1) the myenteric (Auerbach's) plexus within the stroma between the longitudinal and circular muscle laminae of the muscularis layer and (2) the submucosal (Meissner's) plexus of the submucosa of the GI tract. Postganglionic sympathetic nerve fibers from the celiac and superior mesenteric ganglia, located near the aorta, join these plexuses. Preganglionic parasympathetic fibers from the dorsal motor nucleus of the vagus also join these plexuses and terminate within scattered groups of parasympathetic postganglionic neurons whose axons are distributed within the plexuses. General visceral afferent (GVA) nerve fibers within these plexuses are not illustrated; they are the substrate for the autonomous control of gut reflexes exerted by the enteric nervous system in the absence of input from the CNS.

the GI lumen and project by their axon branches in the lamina propria of the mucosa. These sensory neurons can interact with interneurons of Meissner's plexus and of Auerbach's plexus. The axons arising from Meissner's plexus extend both orally and caudally. The neurons of the plexus act as chemical monitors of the environment of the gut lumen and the secretory aspects of gut function. Submucosal sensory cells that project to the mucosa, and collaterals to blood vessels, coordinate functional and vasomotor responses to mucosal signals. The axons of Auerbach's plexus are oriented radially. Some neurons of these gut plexuses are integrated into feedback circuits, with their axons projecting centripetally to the *prevertebral sympathetic ganglia* (*celiac and superior and inferior ganglia located near the aorta),* and these ganglia send fibers back to the gut.

The complex neural organization has a major role in *homeostasis* by the coordinated modulation of gut motility and peristalsis, gut blood vessel tone, fluid transport, and enteroendocrine cell secretion. Meissner's submucosal plexus combines fewer neurons and glia with inner interganglionic connections. Cross talk between the two ganglionic plexuses is subserved by microcircuits comprised of interneurons that remain poorly understood. The ENS synthesizes and is stimulated by virtually all messenger molecules involved in central and peripheral autonomic, endocrine and immune regulation.

Intrinsic Cardiac Nervous System

Recent evidence suggests the existence of a *cardiac nervous system* comparable to the ENS. For example, the presence of interneurons in parasympathetic cardiac ganglia in or near the heart suggests a potential for involvement in reflex reactions that can occur independent of CNS activity (*see* **Fig. 20.3**). This is similar to the role of the parasympathetic ganglia of the ENS. Interneurons within these ganglia can exhibit pacemaker activity that is not generated synaptically, but might contribute to the ongoing activity of other ganglionic neurons. A subset of these interneurons can process input and project output that influences the activity of cardiac muscle. The mechanism in the heart is similar to those of the ENS and the immune system that manifest memory (Rosen and Ploknikov, 2002).

The Enteroendocrine System

The ENS has roles in the motility of the gut, the absorption of nutrients, the rate of proliferation of epithelial cells lining the GI tract, and the release of hormones and neuropeptides by enterochromaffin cells of the *enteroendocrine system*. The substances released by the latter system include such agents as gastric inhibitory peptide (GIP), the neuropeptide motilin, secretin (elicits pancreatic secretion), and cholecystokinen (elicits contraction of the gallbladder). Gastrin stimulates the release of hydrochloric acid by the parietal cells of the stomach and first part of the duodenum. Other cells secrete serotonin that also influences gut motility in the stomach and small intestine. Somatostatin is released by lining cells of the gut. Cells in the intestine secrete GIP, which inhibits gastric secretion. Motilin and substance P are neuropeptides associated with the regulation of intestinal motility. Vasoactive intestinal peptide (VIP) is involved with water and ion secretion as well as intestinal motility.

Enteric Glial Elements Are Supportive and Act in Consort With the ENS as Pacemakers

Enteric neural elements are supported by astrocyte-type enteric glia that have the morphological characteristics of CNS astrocytes. Interstitial cells located between nerve terminals and smooth muscle cells are electrotonically coupled by gap junctions between smooth muscles of the gut. These cells subserve pacemaker slow-wave functions manifested by the intestinal musculature. Based on adult transgenic mouse models, enteric glial cells are essential in maintaining the integrity of the small intestine.

The Peristaltic Reflex

The peristaltic reflex was first recognized as a pressure-evoked descending progressive wave

and attributed to a "local nervous mechanism of the bowel" consisting of oral contraction/anal relaxation. Sensory neurons have long been known to elicit *peristaltic reflex responses* to alterations in the tension in the wall of the gut and in the chemical environment. The expression of the intrinsic neural circuitry within the gut is generally initiated by moderate distention. The reflex persists in vitro in isolation of the dorsal roots, cranial nerve ganglia, and the CNS, indicating that the wall of the bowel contains all of the essential neural elements (i.e., primary sensory neurons, interneurons, and motor neurons to perform normal gut functions).

A peristaltic wave is evoked by an increase in the intraluminal pressure on the luminal surface of the bowel that activates the mechanoreceptors of the surface of the enterochromaffin cells in the epithelial lining of the mucosa. The peristaltic wave, which can occur in the absence of vagal stimulation, is initiated as a response to the following neural sequence. (1) Pressure-evoked stimulation of the receptors of enterochromaffin cells activates them to release serotonin. (2) Serotonin stimulates the intrinsic primary sensory neurons and interneurons that project to the myenteric plexus. (3) This input contributes to stimulating and sustaining rhythms of the peristaltic waves. Two other features are also involved in the intrinsic reflex activity of the gut. (1) Smooth muscle cells, either individually or in groups, exhibit spontaneous waves of electrical depolarization linked to rhythmic contractions. The contractions spread from one muscle cell to another because they are electrotonically coupled by low-resistance gap junctions (Chap. 3). Each wave can occur depending, in part, on the magnitude of depolarization. (2) The fundus of the stomach and first part of the duodenum are two sites in the gut that have roles as pacemakers (equivalent to the pacemakers in the heart). In humans, the basic depolarization rhythm of the pacemaker (a) in the fundus governs the 3 per minute waves of contraction prevalent in the stomach and (b) in the duodenum governs the 11 per minute waves of contraction prevalent in the small intestine.

The overall control and regulation of contractile activity of the gut is not focused at the pacemaker sites, but, rather, is directed to the smooth muscle fibers throughout the gut. The control system effecting this regulation involves (1) the enteric circuitry, (2) the feedback circuits of afferent fibers from the gut to the prevertebral ganglia (located near the aorta) and efferent fibers back to the gut, and (3) influences from the sympathetic and parasympathetic systems. A major role of this system is to act as the coordinator of Starling's "law of the intestine" (e.g., a bolus of food within the intestine initiates a band of constriction proximally and relaxation distally, resulting in a peristaltic wave) by modulating through inhibition the spontaneous rhythmic contractile activity of the gut.

The ENS influences other organ systems, including the prevertebral sympathetic ganglia, and, thus, can coordinate the activity of the GI tract with that of the gallbladder, pancreas, and other organ systems.

Autonomic Innervation of the ENS

Relative to the large numbers of enteric neurons, autonomic inputs are sparse, although potentially powerful in view of their extensive branching patterns. There are impressive sympathetic/parasympathetic innervations of the upper and lower ends of the GI tract and related vasculature. The ENS is involved in tonic and phasic regulation of sympathetic postganglionic norepinephrinergic motor neurons that innervate myenteric and submucosal neurons and those involved in regulating mucosal blood flow (*see* **Fig. 20.5**).

SENSORY AND HUMORAL SYSTEMS

Visceral Sensory Systems

Sensory systems differentially regulate autonomic discharges. The vagus and the splanchnics (greater, lesser, least), and lumbar and pelvic afferent nerves convey information from visceral sensory receptors. Vagal afferents

terminate in the solitary nucleus of the medulla, whereas those in the peripheral nerves traversing the dorsal roots terminate in the dorsal horn and central gray of the spinal cord. Viscerosensory afferents directly or indirectly modulate the activities of the sympathetic and parasympathetic motor systems. Most vagal and sacral afferents respond to distension and contraction

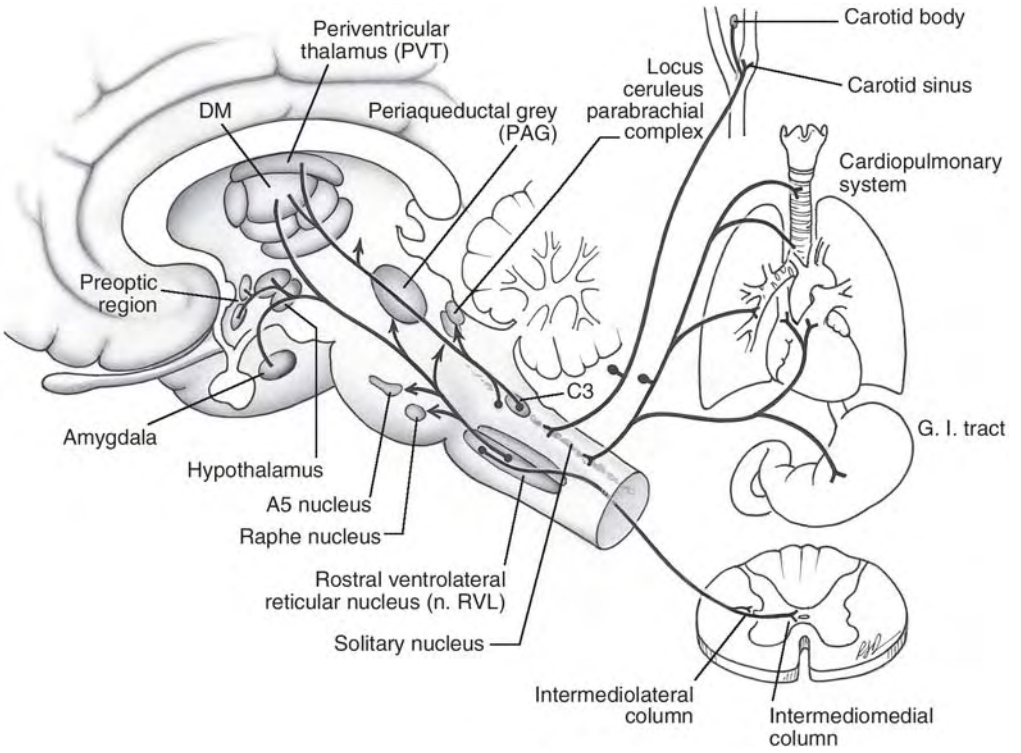


Figure 20.5: Adrenergic nuclei and pathways of the ANS. The adrenergic pathways are activated by homeostatic challenges that mediate compensatory autonomic, endocrine, and behavioral responses. From visceral receptors in the neck (e.g., carotid sinus and carotid body), thorax, and abdomen, the glossopharyngeal and vagus nerves convey inputs to the epinephrinergic solitary nucleus. The adrenergic nuclei of the medulla include the solitary nucleus (C3 and C1) rostral ventrolateral reticular nucleus (nRVL), the norepinephrinergic C1 and C3 groups within the tegmentum, and interneurons of the lateral tegmental field. These medullary nuclei are functionally interconnected with other neuronal centers of the brainstem and cerebrum by two longitudinally oriented pathways: the periventricular tract within the central gray and the (trans)tegmental tract within the reticular formation. These tracts are bidirectional pathways that transmit stress-related information. Generalized arousal states preparatory to sympathetic/defense reactions involve C1 and C3 projections to the norepinephrinergic A5 nucleus, parabrachial nucleus, locus ceruleus, periaqueductal gray, and cerebral centers, including the amygdala, the hypothalamus, the visceral periventricular thalamus of the limbic system, and the dorsomedial thalamic nucleus associated with the mesolimbic network. The nRVL sends fibers to the parasympathetic preganglionic neurons of the dorsal motor nucleus of the vagus and sympathetic preganglionic neurons in the intermediolateral cell column of the spinal cord. The precise roles of the epinephrinergic transmitter network in cardiovascular regulation are uncertain although electrophysiological studies disclose activity patterns that are respiratorily modulated and coupled to the cardiovascular cycle.

of visceral organs, encoding intraluminal activity or volume. Vagal sensory afferents encode baroreceptors, arterial, gastrointestinal, and hepatic chemoreceptors and osmoreceptors, and volume changes in the cardiac atria, lungs, gut, and urinary bladder. Pelvic afferents signal genitourinary pain and inflammation, as well as distension and contraction. Abdominal and pelvic afferents are involved in cardiac–cardiac reflexes, renal–renal reflexes, other organ specific reflexes, and nociceptive reflex circuit functions.

As an example of visceral afferent reflex activity, the cardiovascular system, is regulated by precise visceral sensory reflexes, ensuring that an adequate supply of oxygenated blood is provided to the different body tissues, The afferent monitoring of this homeostatic process is initiated by the receipt (1) of information from *chemoreceptors* about the level of oxygen and carbon dioxide in the blood and (2) of blood pressure information in the arterial system from mechanoreceptors (*baroreceptors*) in the elastic walls of the carotid sinus, heart, and major arteries. The chemoreceptors in the nerve endings in the highly specialized carotid body and the aorta respond directly to the partial pressure of oxygen and carbon dioxide in the blood. The nerve endings in the baroreceptors respond to deformational changes of the elastic walls of the carotid sinus and blood vessels resulting from the forces exerted by changes in blood pressure. The afferent projections from the carotid sinus and carotid body convey information via the glossopharyngeal nerve to the solitary nucleus of the medulla (*see* **Fig. 20.5**).

Effector Organ Responses

The reactions of peripheral tissues and organs *to* sympathetic and parasympathetic activity patterns are defined by the responses of receptors to nerve stimulation. Several general principles apply to autonomic effector organ responses to the evoked release of endogenous neurotransmitters. (1) Sympathetics and parasympathetics are not antagonistic; rather, they act synergistically and differentially under different physiological conditions. The dual hypothesis of antagonism in the ANS is no longer tenable" (Bannister and Mathias, 1999). (2) Organs, as effectors, react predominantly to either sympathetic or parasympathetic activation. (3) Excitatory reactions are the general rule, whereas inhibitory reactions such as relaxation are rare. The iris, heart, and urinary bladder are organs reacting to centrally and peripherally integrated inputs from both systems. Visceral afferents with cell bodies in dorsal root ganglia and vagal and glossopharyngeal sensory ganglia and characterized by unmyelinated or thinly myelinated axons are not associated with a specific system, but exert influences over both systems.

The response of an individual receptor to a specific neurotransmitter is not solely determined by the neurotransmitter; the nature of the receptive sites of the receptor is also a significant factor. The response of an effector is determined by the neurotransmitter–receptor linkages. For, example, norepinephrine stimulates the contraction of smooth muscles of an arteriole (vessel constricts) and the relaxation (dilation) of smooth muscles of the bronchial tubes in the lungs. The different responses to the same neurosecretions are explained by differences in the nature of the receptor sites of smooth muscles. Different neurotransmitters can stimulate different effectors to respond in a similar way. For example, the radial muscle of the iris contracts when stimulated by norepinephrine, whereas the sphincter muscles of the iris contract when stimulated by acetylcholine; both are smooth muscles. **Table 20.1** lists the response of various organs to sympathetic and parasympathetic stimulation. *The diversity of autonomic responses and functions is achieved primarily by different types of receptors for the two classes of postganglionic transmitters: (1) norepinephrine for the sympathetic system and (2) acetylcholine for the parasympathetic system.*

A dual innervation of the body by both the sympathetics and parasympathetics is usual, but not universal. (1) The heart has a true reciprocal innervation (dual) innervation, with the

Table 20.1: Some Comparisons Between the Sympathetic and Parasympathetic Nervous Systems

General		
	Sympathetic nervous system	*Parasympathetic nervous system*
Outflow from CNS	Thoracolumbar levels	Craniosacral levels
Location of ganglia	Paravertebral and prevertebral	Terminal ganglia near effectors ganglia further from effectors
Ratio of preganglionic to postganglionic neurons	Each preganglionic neuron synapses with many postganglionic neurons	Each preganglionic neuron synapses with a few postganglionic neurons
Distribution in body	Throughout the body	Limited primarily to viscera of head, thorax, abdomen, and pelvis
Specific Structures		
Structure	*Sympathetic function*	*Parasympathetic function*
Eye		
Radial muscle of iris	Dilates pupil (mydriasis)	
Sphincter muscle of iris		Contraction of pupil (miosis)
Ciliary muscle (accommodation)	Relaxation for far vision	Contraction for near vision
Glands of head		
Lacrimal gland		Stimulates secretion
Salivary glands	Scanty thick, viscous secretion	Profuse, watery secretion
Heart		
Rate	Increase	Decreases
Force of ventricular contraction	Increase	
Blood vessels	Generally constricts[a]	Slight effect
Lungs		
Bronchial tubes	Dilates lumen	Constricts lumen
Bronchial glands		Stimulates secretion
Gastrointestinal tract		
Motility and tone	Inhibits	Stimulates
Sphincters	Stimulates	Inhibits (relaxes)
Secretion	May inhibit	Stimulates
Gallbladder and ducts	Inhibits	Stimulates
Liver	Glycogenolysis increase (blood sugar)	
Adrenal medulla	Secretion of epinephrine and norepinephrine[a]	
Sex organs	Vasoconstriction, constriction of vas deferens, seminal vesicle, and prostatic musculature (ejaculation)	Vasodilation and erection
Skin		
Sweat glands	Stimulated[a]	
Blood vessels	Constricted	Slight effect
Neurotransmitter at neuroeffector junction	Usually norepinephrine[a]	Acetylcholine
Inactivation of transmitter	Slow and reuptake	Rapid

[a] Exceptions: Some postganglionic neurons of the sympathetic nervous system are cholinergic neurons. Sympathetic neuroeffector transmission mediated by acetylcholine includes (1) some blood vessels in skeletal muscles and (2) most sweat glands. The postganglionic sympathetic neurons that innervate the sweat glands are, before innervating the sweat glands, adrenergic neurons. Following the innervation of the sweat glands they become cholinergic neurons (see section concerning neural specificity and plasticity, Chap. 6). The sweat glands of the palm are innervated by adrenergic neurons. The cells of the adrenal medulla are actually postganglionic cells: they are innervated by preganglionic cholinergic sympathetic neurons,

sympathetics acting to increase the rate of the heart beat and the parasympathetics acting to decrease it. (2) The salivary glands are innervated synergistically, with sympathetic activity producing a thick, viscous secretion and parasympathetic producing a profuse, aqueous secretion. (3) The constriction and dilatation of the pupil exemplifies an activity resulting from the stimulation of different muscle groups. The pupil of the eye dilates when the radial (dilator) muscles innervated only by sympathetic fibers are stimulated and it constricts when the sphincter (constrictor) muscles innervated only by parasympathetic fibers are stimulated. (4) Some structures are only innervated by one system: Hair muscles (erector pili muscles that produce goose pimples), sweat glands, and most arterial blood vessels are stimulated only by sympathetic fibers (*see* **Fig. 20.2**).

An autonomic neuron can exhibit a functional form of plasticity by modifying or altering its transmitter or receptor sensitivity during development and aging (Chap. 6). For example, the postganglionic sympathetic fibers innervating the sweat glands in the human are functionally adrenergic before birth and become cholinergic postnatally.

Cotransmission of Nonadrenergic and Noncholinergic Transmitters in the ANS

Over 10 putative transmitters and modulators have been identified and added to the classical autonomic transmitters, norepinephrine, and acetylcholine. These neuroactive nonadrenergic and noncholinergic (NANC) agents are active in neurotransmission at synapses of sympathetic, parasympathetic, and enteric neurons. Most autonomic neurons contain two to several agents, including acetylcholine, amino acids, biogenic amines, neuropeptides, and others (Chap. 15). The current thesis is that many, if not all, neurons of the ANS store and release more than one agent. Note the large vesicles containing a neuropeptide and small vesicles containing norepinephrine in the varicosities in **Fig. 15.4**. For example, acetylcholine and VIP are cotransmitters of the parasympathetic fibers innervating the salivary glands, with the former increasing salivary secretion and the latter acting as a modulator. Another example is the presence of neuropeptide Y (NPY) in sympathetic vasoconstrictor axons, which potentiates the action of norepinephrine on the contractile apparatus of smooth muscle. Vagal-induced slowing of the heart is inhibited by NPY, which is released by increased sympathetic activity. Constituents of the prevertebral sympathetic ganglia include small intensely fluorescent (SIF) cells, containing monoamines and neuropeptides. The cotransmission of specific combinations of transmitters and modulators has been suggested as a form of chemical coding, especially in the enteric system.

The purinergic transmitters responsible for most NANC inhibition are ATP or related purine compounds such as adenosine (Chap. 15). The nitrergic transmitter responsible for some NANC inhibition is the free-radical nitric oxide (NO) (Chap. 15).

CENTRAL AUTONOMIC CONTROL CIRCUITS

Central autonomic control circuits coordinate autonomic functions and the ongoing behavioral needs of the organism through the activities of the somatomotor, endocrine, and autonomic systems. These systems are represented in overlapping regions of the brain. The behavioral strategies and reflex mechanisms within these circuits act in the defense of the organism and in homeostasis, which are coordinated by interconnected groups of nuclei in the brainstem and higher forebrain centers.

Three of the key components of the central autonomic control circuits are the *solitary nucleus*, which receives visceral sensory information, the *hypothalamus,* which is the most important neural center in the overall control of visceral and endocrine functions, and the *rostral ventrolateral reticular nucleus* (n RVL), a major relay motor nucleus regulating the autonomic nervous system (*see* **Fig. 20.5**). The solitary nucleus is the major recipient of visceral afferent inputs including taste. Afferent infor-

mation is, in turn, utilized to modulate several autonomic functions such as cardiovascular reflexes, which are discussed later in the chapter. The hypothalamus is the master visceral control center in the regulation of many autonomic and endocrine responses and in homeostasis generally (Chaps. 21 and 22). The adrenergic nRVL regulates autonomic responses (1) via projections both to the preganglionic neurons of the dorsal motor nucleus of the vagus of the parasympathetic system and to the preganglionic neurons of the intermediolateral nuclei of the sympathetic system and (2) via rostral projections to higher centers of the brain through the periventricular and the tegmental tracts of the brainstem (*see* **Fig. 20.5**).

The nuclei forming the extensive central autonomic control network within the brainstem and forebrain are linked together and integrated by two bidirectional pathways: the *(trans)tegmental tract* within the reticular formation and the *periventricular tract* within the central gray matter (*see* **Fig. 20.5**). The core nuclei of this network comprise the parabrachial nucleus and the periaqueductal gray of the brainstem, the hypothalamus, the amygdala of the limbic system, the visceral sensory thalamic nuclei (Chap. 23), and visceral areas of the cerebral cortex (Chap. 25). Critical modulating influences on the central autonomic network are made by brainstem noradrenergic cell groups (e.g., A1), adrenergic cell groups (e.g., C1 and C3), serotonergic raphe nuclei, and interneurons within the nRVL. These central autonomic control circuits are functionally endogenous. The basic performance of their roles can be performed in the absence of hypothalamic control.

The general organization of the central autonomic network is illustrated in **Fig. 20.5**. The solitary nucleus receives afferent fibers from visceral receptors located in the taste buds, carotid body, carotid sinus, and many other locations associated within the array of visceral organs. The solitary nucleus and its relay nRVL send outputs to autonomic circuits via two general routes: One is a focused relatively simple reflex circuitry and the second is a multidimensional complex circuitry. In the first, information is directed locally into lower brainstem visceral circuits such as the cardiovascular and respiratory centers. In the second, information is directed to the more extensive and complex circuitry of the upper brainstem and forebrain components of the central autonomic control network (*see* **Fig. 20.6**). The latter is integrated into behavioral responses associated, for example, with the limbic system (Chap. 22).

The central autonomic control nuclei and centers are interconnected by the tegmental tract and periventricular tract to and from the parabrachial nucleus, periaqueductal gray, and such forebrain structures as the hypothalamus, amygdala, visceral sensory centers, and areas of the thalamus and neocortex (*see* **Fig. 20.5**). In addition, neural interconnections between these structures result in interactions directed to the hypothalamus. The following are examples of some functional correlates associated with these centers.

Visceral sensory information derived from the solitary nucleus is relayed to the *parabrachial nucleus,* which acts as a key brainstem processor projecting to and receiving communications from the periaqueductal gray and forebrain centers. The parabrachial nucleus has a functional role in behavioral responses to various visceral sensations including taste as is indicated by the prevention of previously conditioned behavioral responses to gustatory cues in rodents following its destruction.

The periaqueductal gray is a processor. (1) Its projections to the *lateral tegmental receptive field (LTF) of the medulla* modulate actions associated with changes in blood pressure and heart rate through cardiovascular reflexes. The resulting "fight or flight" response results in reducing the amount of blood flow directed to the viscera and increasing blood flow to the lower extremities to enhance sustained running behaviors. (2) Its projections to the substantia nigra and the extrapyramidal system result in the agonizing facial contortions of a marathon runner during the last miles of a race.

The *amygdala* of the limbic system is involved in many autonomic responses with

specific behaviors (Chap. 22). For example, a rat is conditioned to link an auditory cue with an unpleasant electric shock, which causes an elevated heart rate. In a short time, just the auditory cue suffices to evoke this response, but a lesion of the central nucleus of the amygdala blocks it (LeDoux, 2002). This amygdaloid nucleus projects to the hypothalamus and the lateral tegmental field (LTF) in the medulla.

Functional Neuroanatomy of Autonomic Control Centers in the Medulla (*see* Fig. 20.6).

Autonomic regulatory mechanisms of the medulla are of critical importance for the reflex control of the cardiovascular system. The struc-

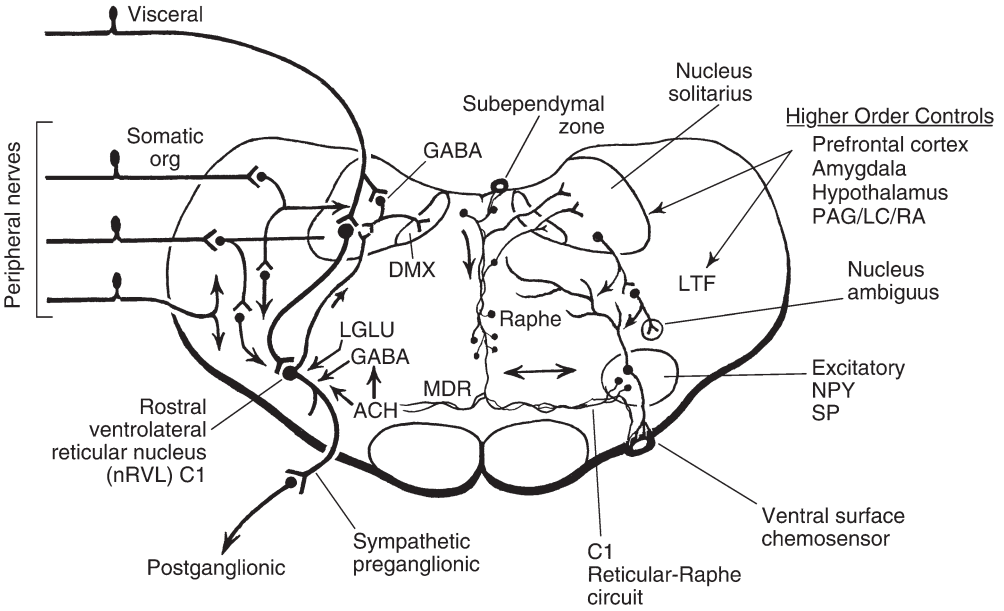


Figure 20.6: Visceral reflex circuits of the medulla. The circuits within the medulla are essential for the maintenance of visceral (servo-control) reflexes that regulate, among others, the cardiovascular system. Visceral afferent stimuli transmit by the vagus and glossopharyngeal nerves to the solitary nucleus which synapses in the lateral tegmental field (LTF) of the reticular formation (upper left arrow). Other afferent and central inputs converge on the LTF from (1) trigeminal, vestibular, and spinal dorsal horn relay nuclei and (2) from higher centers of the brainstem and cerebrum via the periventricular tract and the tegmental tract (upper right arrow). Following the ongoing central integration of the convergent sensory information, the LTF interacts with circuits modulating cardiovascular reflexes. These comprise the network of reticular formation interneurons, including the medial "vasodepressor" region (MDR) and the "vasopressor" (sympathetic premotor) region of the nRVL. In addition, information is derived from suspected chemoreceptor sensors on the dorsal and ventral medullary surfaces. Myriad transmitter modulators of the visceral nuclei include glutamate and GABA. Note the projection (arrow) from the nRVL to the solitary nucleus indicative of servo-control systems exerting feedback controls by the nRVL ultimately over the sympathetic and parasympathetic outflows. The relay nRVL acts as the final common pathway projecting centrally integrated information (1) via short circuits to the parasympathetic preganglionic neurons of the dorsal motor nucleus of the vagus and ambiguus nucleus and (2) via the descending reticulospinal tracts to preganglionic neurons of the sympathetic system (center arrow).

tural and functional integrity of the medullary circuitry is essential in sustaining life by its tonic and phasic regulation of the cardiovascular system involving both sympathetic and parasympathetic activity patterns. Visceral reflexes involve servo-control corrections via feedback signals such as between the motor and sensory components. (Note in **Fig. 20.6** the feedback arrow between the relay motor nRVL and the sensory solitary nucleus.) Visceral and somatic afferents transmit input over spinal and cranial nerves to the dorsal horn and solitary nucleus. Substantial visceral and somatic afferent inputs from the solitary nucleus, dorsal horn, and trigeminal and vestibular relay nuclei are directed to the LTF, which is a *sensory convergent field* within the lateral tegmentum of the medulla (*see* **Fig. 20.6**).

Much of the visceral sensory outflow from the solitary nucleus is directed rostrally via the tracts of the bidirectional *periventricular* and tegmental pathways to the upper brainstem and forebrain centers of the central autonomic control network involved in mediating behavioral responses. Of these, the hypothalamus has a broad reach, in that it modulates both visceral responses and endocrine activity. In general, the higher centers communicate via descending tracts within the bidirectional *periventricular* and *tegmental pathways* with the parabrachial nucleus and the *convergent sensory fields* in the LTF. Joining these convergent fields are inputs from probable chemoreceptive vascular regions on both the dorsal and ventral medullary surfaces of the medulla (*see* **Fig. 20.6**).

Brainstem and forebrain centers participate in the modulation of the dynamics of the cardiovascular system. For example, the visceral sensory (anterior insula) cortex interacts with anterior cingulate visceral motor areas (limbic system). Electrical stimulation of the latter can produce several visceral responses, including changes in blood pressure. A likely cause of these pressure changes results from communication via the central control circuitry that activates the sensory convergent field of the medulla followed by the responses of the cardiovascular reflex.

The sensory convergent LTF receives information directly from the periphery via the solitary nucleus and its terminal field and indirectly from higher centers in the brainstem and forebrain (*see* **Fig. 20.6**). In turn, the LTF acts as a control center exerting regulatory influences over autonomic discharge patterns generated in activity centers within the medial vasodepressor region (MDR) and the vasopressor (sympathetic premotor) region near the nRVL in the reticular formation. These visceral and semiautonomic reflexes are mediated by relays to the nRVL, which serves as the final common pathway (gateway) by which centrally integrated information is used to regulate the outflow of the ANS with regard to the demands of all stressors.

Autonomic Regulation of Cardiovascular Functions

This account of the fundamentals of central autonomic control focuses on brainstem regulation of the cardiovascular system (CVS). The brainstem and forebrain centers participate in the modulation of the dynamics of this CVS system, and its long term stability is dependent on its integrated neural and humoral mechanisms. Much of the control of cardiodynamics is reflexive. The heart beat is initiated not by the central nervous system but by the heart's sinoauricular pacemaker. The heart, unlike the blood vasculature vessels, receives dual sympathetic and parasympathic (vagal) innervation. Cardiovascular reflex arcs powerfully modulate heart rate and actively depress heart rate in the resting state.

The medulla oblongata (**Fig. 20.5**). The integrity of medulla oblongata is essential in sustaining life. Consciousness, awareness of perceptions, and the drives to adapt are dependent on the functional integrity of pontomedullary reticular formation exerting tonic and phasic influences over sympathetic and parasympathetic nerve activity patterns. Cardiorespiratory circuits coordinate rhythmic breathing and heart rate, maintaining blood pressure volume, normal oxygenation, and acid–base balance. Behavioral regulation of

breathing has its expression in speech in as well as in nonverbal and emotional expressions. Coordinated activity of a diffuse network of neurons in the visceral emotional brain exerts a major influence over the autonomic control circuit of the medulla. Sensory systems and centrally generated signals converge on the lateral reticular core, shaping (driving) basal sympathetic nervous system discharge to the cardiovascular system, adrenal gland, and other viscera.

Somatic and visceral autonomic control (**Figs. 20.4** and **20.5**). Somatic and visceral afferents transmit over spinal and cranial nerves to the spinal dorsal horn and the nucleus of the solitary tract. The spinal dorsal horn projects to somatic and autonomic neurons in ventral and lateral horns of the spinal cord, respectively, forming local reflex circuits. General viscerosensory cranial and spinal somatovisceral nerves transmit to the solitary nucleus, which projects locally to autonomic control regions of lateral and medial reticular formation and pontine parabrachial complex forming a reciprocally organized "rapid response" network. Somatic and visceral sensory relay systems target arrays of reticular interneurons in the multi-sensory receptive region of the lateral tegmental field (LTF). Higher centers in the brainstem and forebrain converge on LTF (**Fig. 20.6**). In turn, the LTF acts as a control center, exerting regulatory influences over autonomic discharge patterns generated in activity centers within the "medial vasodepressor region" (MDR) and the "vasopressor" (sympathetic premotor) region near the rostral ventrolateral nucleus (n. RVL) in the reticular formation. Counter-regulatory influences are exerted over autonomic nerve discharges to internal organ systems.

The LTF and its sympathetic premotor center. Visceral and somatoautonomic reflexes are mediated by the LTF and cardiorespiratory neurons in the n. RVL. Evidence suggests that the LTF, by integrating peripheral and central information, exerts major influence over the n. RVL, which directly projects to all sympathetic preganglionic cell columns. The n. RVL serves as a final common pathway (gateway) for centrally integrated peripheral information to act upon the sympathetic nervous system, while exerting feedback influence over craniosacral parasympathetic tone. The LTF, a sensory convergence zone, may be in a pivotal position to exert influence over n. RVL sympathetic premotor neurons. This key intrareticular circuit is implicated in maintaining resting discharges of sympathetic nerves and resting arterial blood pressure and heart rate. The n. RVL synthesizes epinephrine on physiological demand, and is excited by emotional visceral distress, triggering global emotional visceral defense reactions. The n. RVL differentially and simultaneously coordinates sympathetic and parasympathetic stress response.

DENERVATION SENSITIVITY AND SYMPATHECTOMY

Somatic effectors are dependent on their innervation to maintain structural and functional integrity. When denervated, they eventually atrophy. This is the fate of denervated voluntary muscles as noted in a lower motor neuron paralysis (Chap. 12). Autonomic effectors are not wholly dependent on their innervation. Denervated involuntary muscles, cardiac muscle, and glands continue to function. For example, the transplanted heart may function reasonably well. However, when deprived of autonomic nervous system influences, these effectors are abnormal in that they do not respond as effectively as they should to satisfy the changing demands of the organism.

When an effector is deprived of its innervation, it may become extremely sensitive to chemical mediators (neurotransmitters). For example, the rate of beat of the totally denervated heart will increase if the heart is exposed to just 1 part of epinephrine in 1400 million. This denervation hypersensitivity is lost following regeneration of the fibers and reinnervation of the heart. Denervation hypersensitivity is noticeable in clinical situations following sympathectomy. In Horner's syndrome, the pupil of

one eye is constricted and does not normally dilate because it is deprived of sympathetic stimulation. However, when a patient with Horner's syndrome is extremely excited, the epinephrine and norepinephrine released by the adrenal medulla can stimulate the hypersensitive denervated dilator muscle of the iris to respond so that the pupil dilates; this is known as the *paradoxical pupillary response.*

NEURAL CONTROL OF THE URINARY BLADDER

The urinary bladder is predominately under parasympathetic control. The motor limb of the voiding reflexes comprises the parasympathetic contraction of the detrusor muscle (collective term for the bundles of smooth muscle forming the muscular wall of the bladder) stimulated by cholinergic and purinergic transmitters. This is coordinated with the parasympathetic relaxation of the musculature of the proximal urethra modulated by nitrergic messengers (Chap. 15). In addition, there is adrenergic sympathetic control over the proximal urethral musculature that results in its constriction during emission and ejaculation. This prevents retrograde ejaculation into the bladder. Thus, the sympathetic and parasympathetic nervous systems function both antagonistically and synergistically to complement their physiological activities. In addition, the somatosensory and motor pathways are involved in the volitional control of storage of urine in the bladder during urination. The CNS integrates behaviors and pelvic organ functions via the *pontine micturition center (PMC)* or *Barrington's nucleus*, which is located anteromedial to the locus ceruleus and lateral to the laterodorsal tegmental nucleus (**Fig. 20.5**). The connections of the PMC with the central regulators lead to the integrated process resulting in parasympathetic sphincteric control of many pelvic visceral structures (e.g., distal colon and, of most importance, control of the detrusor muscle). PMC axons branch to innervate the locus ceruleus, a major arousal/attentional center, which promotes vigilance during micturition. PMS projections to the "behavioral inhibitory region" of the periaqueductal gray may facilitate the state of calm during elimination.

MEGACOLON (HIRSCHSPRUNG'S DISEASE)

In this condition in young children, a portion of the large bowel is constricted, while the colon proximal to the obstructed segment is enormously dilated. The constricted segment contains the flaw responsible for the disease—intrinsic neurons of the intramural plexuses are missing, rendering this aganglionic segment unable to relax. However, the region has an autonomic innervation consisting of both cholinergic and adrenergic axons, thus illustrating the significance of the intrinsic neurons in peristalsis.

SUGGESTED READINGS

Agassandian K, Fazan VP, Adanina V, Talman WT. Direct projections from the cardiovascular nucleus tractus solitarii to pontine preganglionic parasympathetic neurons: a link to cerebrovascular regulation. *J. Comp. Neurol.* 2002;452:242–254.

Appenzeller O. *Clinical Autonomic Failure: Practical Concepts.* 5th ed. New York: Elsevier.;1986.

Appenzeller O, Oribe E. *The Autonomic Nervous System: An Introduction to Basic and Clinical Concepts.* 5th ed. New York: Elsevier.; 1997.

Bannister R. Treatment of autonomic failure. *Curr Opin. Neurol. Neurosurg.* 1992;5:487–491.

Bannister R, Mathias CJ, eds. *Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System.* New York: Oxford University Press; 1999.

Benarroch EE. *Central Autonomic Network: Functional Organization and Clinical Correlations.* Armonk, NY: Futura; 1997.

Blessing W. *The Lower Brainstem and Bodily Homeostasis.* New York: Oxford University Press; 1997.

Bloom FE. Neuropeptides. *Sci. Am.* 1981;245: 148–168.

Bolis L, Licinio J, Govoni S. *Handbook of the Autonomic Nervous System in Health and Disease.* New York: Marcel Dekker; 2003.

Brading A. 1999. *The Autonomic Nervous System and its Effectors.* Malden, MA: Blackwell Science.

Brown M, Tache Y. Hypothalamic peptides: central nervous system control of visceral functions. *Fed. Proc.* 1981;40:2565–2569.

Burnstock G, Hoyle CHV. *Autonomic Neuroeffector Mechanisms.* Philadelphia, PA: Harwood Academic; 1992.

Burnstock G, Sillito AM. 2000. *Nervous Control of the Eye.* Amsterdam: Harwood Academic.

Cannon W. *The Wisdom of the Body.* New York, WW Norton; 1932.

Cortelli P, Pierangeli G. Chronic pain–autonomic interactions. *Neurol. Sci.* 2003;24(Suppl. 2): S68–S70.

Elfvin LG, Lindh B, Hokfelt T. The chemical neuroanatomy of sympathetic ganglia. *Annu. Rev. Neurosci.* 1993;16:471–507.

Fisher LA, Brown MR. Neuropeptides and the autonomic nervous system. *Psychother. Psychosom.* 1993;60:39–45.

Furness JB. Intestinofugal neurons and sympathetic reflexes that bypass the central nervous system. *J Comp. Neurol.* 2003;455:281–284.

Furness JB, Clerc N, Kunze WA. Memory in the enteric nervous system. *Gut* 2000;47(Suppl. 4): iv60–iv62.

Gershon MD. *The Second Brain: The Scientific Basis of Gut Instinct and a Groundbreaking New Understanding of Nervous Disorders of the Stomach and Intestine.* New York: HarperCollins; 1998.

Goldstein DS. *The Autonomic Nervous System in Health and Disease.* New York: Marcel Dekker; 2001.

Grazzi L, Bussone G. Effect of biofeedback treatment on sympathetic function in common migraine and tension-type headache. *Cephalalgia* 1993;13:197–200.

Guillemin R. Control of adenohypophysial functions by peptides of the central nervous system. *Harvey Lect.* 1978;71:71–131.

Harris-Warrick RM. *Dynamic Biological Networks: The Stomatogastric Nervous System.* Cambridge, MA: MIT Press; 1992.

Hess WR. *Diencephalon: Autonomic and Extrapyramidal Functions.* New York: Grune & Stratton; 1954.

Hoyle CHV, Lincoln J, Burnstock G. Neural control of pelvic organs. In: Rushton DN, ed. *Handbook of Neuro-urology.* New York: Marcel Dekker; 1994:1–54.

LeDoux JE. *Synaptic Self: How Our Brains Become Who We Are.* New York: Viking, 2002.

Levenson RW. Blood, Sweat, and Fears: The Autonomic Architecture of Emotion. *Ann. NY Acad. Sci.* 2003;1000:348–366.

Loewy AD, Spyer KM. *Central Regulation of Autonomic Functions.* New York: Oxford University Press; 1990.

Miller NE. Biofeedback and visceral learning. *Annu. Rev. Psychol.* 1978;29:373–404.

Milner P and Burnstock G. *Neurotransmitters in the autonomic nervous system.* In: Korczyn, ed. *Handbook of Autonomic Nervous System Dysfunction.* New York: Marcel Dekker; 1995.

Robertson D, Baggioni I, Burnstock G, Low P, eds. *Primer on the Autonomic Nervous System.* 2nd ed. San Diego: Elsevier, Academic, 2004; pp. 1–457.

Rosen M, Plotnikov A. The pharmacology of cardiac memory. *Pharmacol Ther.* 2002;94:63–75.

Ruggiero DA, Underwood MD, Mann JJ, Anwar M, Arango V. The human nucleus of the solitary tract: visceral pathways revealed with an "in vitro" postmortem tracing method. *J. Auton. Nerv. Syst.* 2000;79:181–190.

Saper CB. The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. *Annu. Rev. Neurosci.* 2002;25: 433–469.

Sved AF, Ito S, Sved JC. Brainstem mechanisms of hypertension: role of the rostral ventrolateral medulla. *Curr. Hypertens. Rep.* 2003;5:262–268.

Webster JI, Tonelli L, Sternberg EM. Neuroendocrine regulation of immunity. *Annu. Rev. Immunol.* 2002;20:125–163.

Welch M, Keune J, Welch-Horan T, Anwar N, Anwar M, Ruggiero D. Secretin activates visceral brain regions in the rat including areas abnormal in autism. *Cell. Mol. Neurobiol.* 2003;23:817–837.

21 Hypothalamus

General Functional Considerations
Basic Circuits of the Hypothalamus
Neurohumoral Reflexes
Influences on the Autonomic Nervous System
Temperature Regulation
Regulation of Water Balance
Food Intake and Energy Balance
Expressions of Emotion and Behavior
Circadian Rhythms
The Circumventricular Organs

The hypothalamus functions primarily in homeostasis (the maintenance of a relatively constant internal body environment). Its effects are exerted through the autonomic nervous system, the endocrine system, and the somatic motor system. Its influence is widespread and is even involved with emotions and behavior.

The 4-g hypothalamus is located in the basal region of the diencephalon adjacent to the third ventricle. In its rostrocaudal extent from the lamina terminalis to the midbrain, the hypothalamus is divided into nuclei and four major areas (*see* **Figs. 21.1 and 21.2**): (1) a rostral or preoptic area, (2) a supraoptic area located above the optic chiasma, (3) a tuberal area (the region of tuber cinereum extends from optic chiasma to the mammillary body), and (4) a caudal or mammillary area that grades into the midbrain central gray. The *hypophysis* (pituitary gland) extends ventrally from the tuberal area. Some important hypothalamic nuclei include the suprachiasmatic nucleus of the preoptic area, the paraventricular nucleus and supraoptic nucleus of the supraoptic area, the lateral and ventral nuclei of the tuberal area, and the mammillary nuclei of the mammillary area. Developmentally, the preoptic area is a telencephalic structure, whereas the rest of the hypothalamus is diencephalic. The preoptic area is so closely associated with the hypothalamus, however, that it is considered a part of the hypothalamus.

The hypophysis (pituitary gland) comprises two major subdivisions: the *adenohypophysis* (an epithelial structure) and the *neurohypophysis* (a neural structure). The adenohypophysis develops as an outpocketing from the embryonic pharynx, whereas the neurohypophysis originates as an outgrowth from the region of neural tube giving rise to the hypothalamus. The adenohypophysis consists of the pars distalis (anterior lobe), pars tuberalis, and pars intermedia (*see* **Fig. 21.1**). The neurohypophysis comprises the median eminence of the tuber cinereum, infundibular stem, and infundibular process (pars nervosa, neural lobe). The median eminence, which extends from the optic chiasma to the infundibular stem, differs from the rest of the hypothalamus. The median eminence and the infundibular stem are known as the *hypophysiotropic area*, where the neurally derived hypothalamic- releasing hormones are released and transferred to the hypophyseal portal system (*see* **Fig. 21.2**).

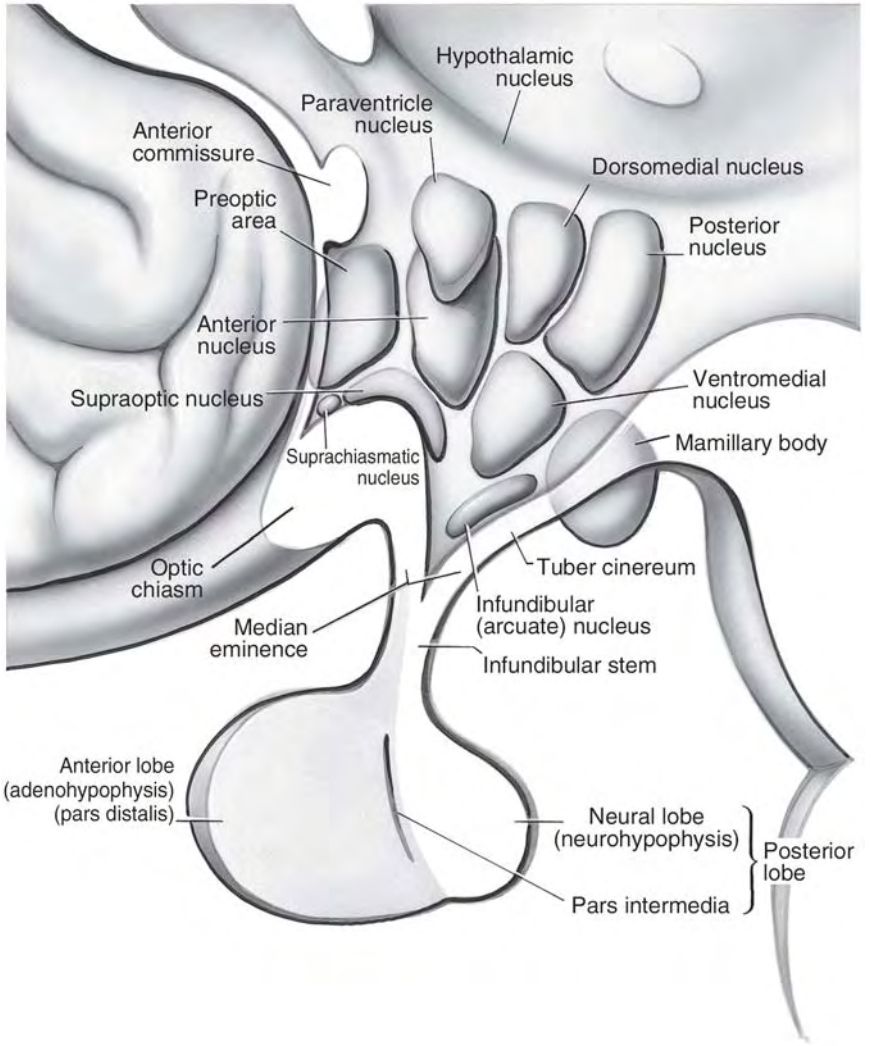


Figure 21.1: Some hypothalamic nuclei and the hypophysis. The hypothalamus is composed of four nuclear areas: (1) the rostral or preoptic area, including the suprachiasmatic nucleus; (2) the supraoptic area, including the supraoptic, anterior, and paraventricular nuclei; (3) the tuberal area, including the infundibular, ventromedial, and dorsomedial nuclei; and (4) the caudal or mammillary area, including the posterior nucleus and mammillary body.

GENERAL FUNCTIONAL CONSIDERATIONS

The hypothalamus acts (1) to integrate somatic, visceral, and behavioral information from the internal and external environment and use it (2) to coordinate the autonomic and endocrine outflow with the behavioral status of the organism. The hypothalamus coordinates the behavioral and emotional responses generated in the forebrain. The processed information is sent via neural pathways to control centers in the brainstem that mediate ongoing metabolic activities needed to produce coordinated autonomic control and

behavior. These pathways include (1) the laterally located medial forebrain bundle and (2) the medially located periventricular circuits with the periaqueductal gray of the midbrain (*see* **Figs. 21.3 and 21.4**). An additional route involves the vascular portal system coordinating the hypothalamus with the pituitary gland. In essence, the hypothalamus functions to integrate autonomic and endocrine responses with behaviors, especially those concerned with the homeostatic requirements of everyday life.

The hypothalamus integrates and controls the following essential functions:

1. Regulation of body temperature via activities ranging from the control of metabolic thermogenesis to behaviors such as wearing garments appropriate for given weather conditions
2. Regulation of blood pressure and electrolyte composition—via mechanisms ranging from control of fluid intake and salt appetite to blood osmolality and vasomotor tone.
3. Regulation of energy metabolism via control of food intake, digestion, and the metabolic rate.
4. Regulation of reproduction via control of hormones, pregnancy, and lactation.

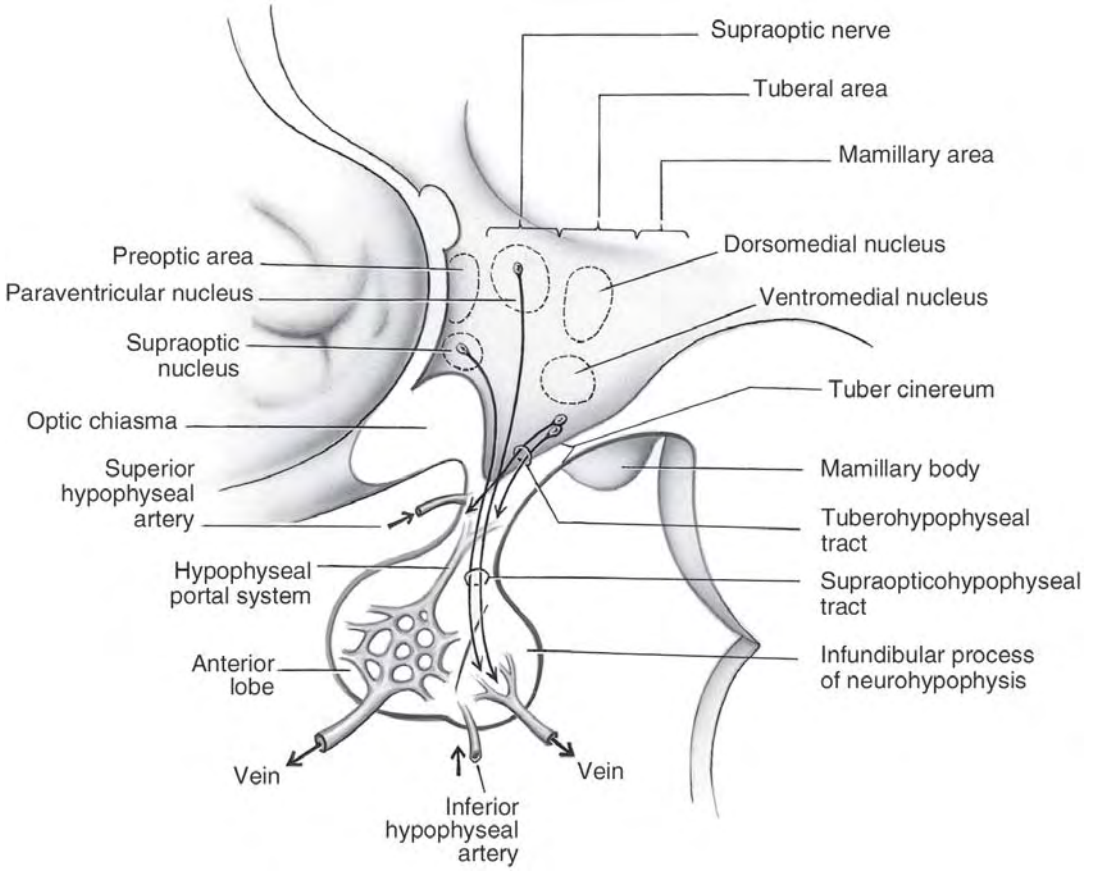


Figure 21.2: Some hypothalamic nuclei and the hypophysis. The supraopticohypophyseal tract extends from the supraoptic and paraventricular nuclei to the capillary bed of the neurohypophysis. The hypophyseal–portal system is a vascular network extending from the base of the hypothalamus and upper neurohypophysis to the anterior lobe of the hypophysis.

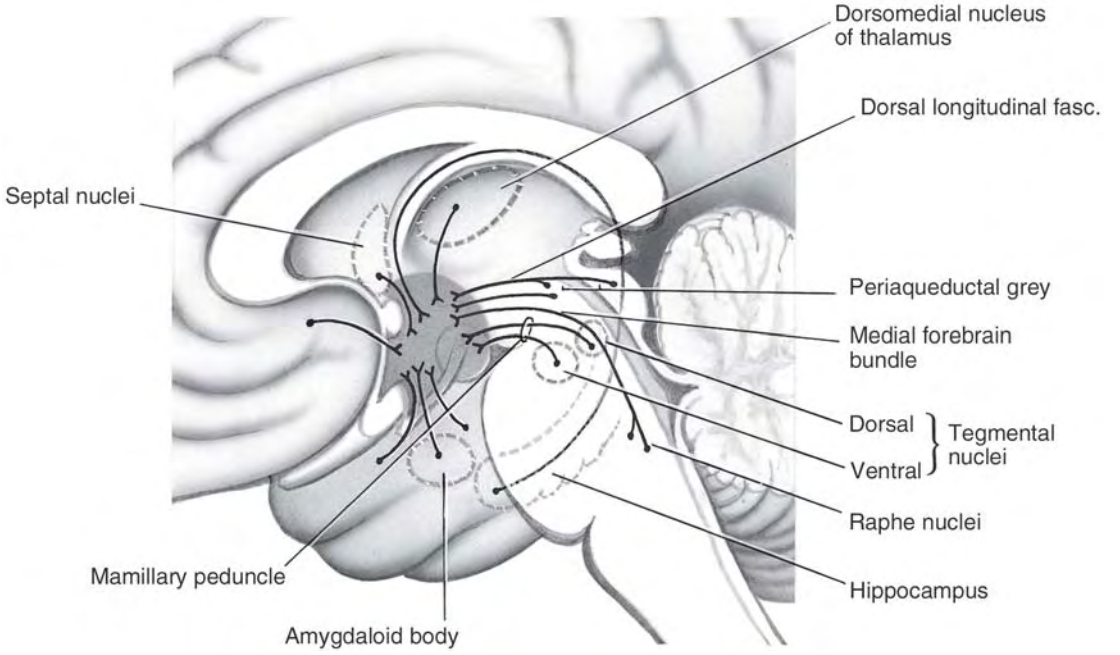


Figure 21.3: The major tracts conveying input to the hypothalamus.

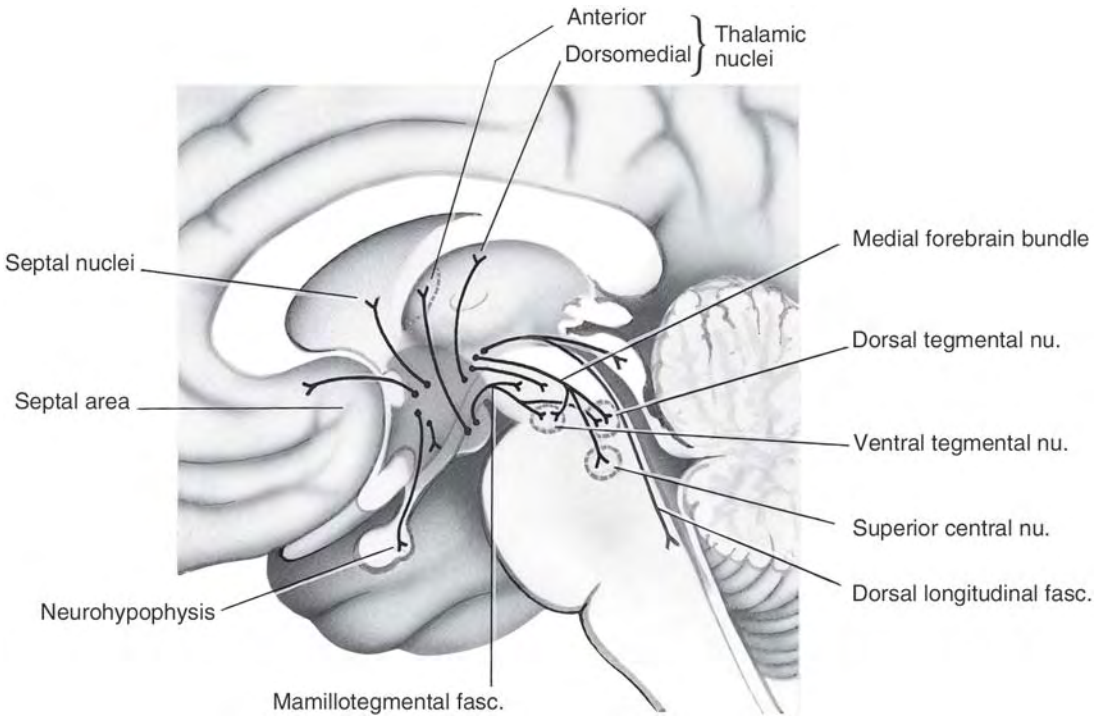


Figure 21.4: The major tracts conveying output from the hypothalamus.

5. Regulation of emergency responses (e.g., physical and immunological) to stress via control of blood flow to muscle and other tissues and the release of adrenal stress hormones such as cortisol.

Intrinsic Hypothalamic Receptors

Some neurons within the hypothalamus act as intrinsic receptors involved in several vital functional activities: thermal receptors for temperature regulation and osmoreceptors for water metabolism. For example, hypothalamic receptors monitor the temperature of the blood flowing through the hypothalamic capillaries, enabling the organ to perform its role as the integrator of body temperature. The efferent limb of the reflex includes (1) descending autonomic pathways to the sweat glands and peripheral blood vessels and (2) descending somatic pathways to the trunk musculature for panting and shivering.

Neurohumoral Reflexes

The neurohumoral reflex arc utilizes both the nervous system (neuro) and the blood vascular system (humoral). To perform its role in water metabolism, for example, the hypothalamus utilizes an intrinsic hypothalamic receptor to monitor the osmolality of the blood flowing through the brain. The neuronal receptors are stimulated to release a neurosecretion, antidiuretic hormone (ADH), which is conveyed via nerve fibers (*supraopticohypophyseal tract*) to the infundibular process of the hypophysis (*see* **Fig. 21.2**), where it is stored and released into the systemic blood system and conveyed to its target structures in the kidney. Such reflexes are discussed more fully below.

Hypophyseal Portal System and Hypothalamic-Releasing Hormones

The hypophysis receives its blood supply from several arteries (*see* **Fig. 21.2**). A pair of inferior hypophyseal arteries from the internal carotid arteries furnishes blood to the infundibular process and infundibular stem. Several superior hypophyseal arteries from the internal carotid arteries form a capillary plexus in the median eminence, pars tuberalis and infundibular stem; this capillary plexus collects into the hypophyseal portal system of blood vessels (hypothalamic portal system and hypophyseal portal vein). This portal system is a vascular network commencing as a capillary bed in the median eminence and collecting into several main channels before arborizing into a capillary (sinusoidal) bed in the adenohypophysis.

The hypophyseal portal system is the vascular pathway through which the neural language from the hypophysiotropic area, in the form of releasing hormones (RH), is transferred and conveyed to the pars anterior to trigger the endocrine language of the hypophysis. More specifically, the hypothalamic nerve fibers liberate the releasing hormones from these nerve endings into the capillary plexuses of the median eminence and infundibular stem; these hormones are conveyed through the hypophyseal portal vessels to the adenohypophysis, where they stimulate or inhibit the release of a number of the hypophyseal hormones (*see* "Releasing Hormones").

BASIC CIRCUITS OF THE HYPOTHALAMUS

The hypothalamus is strategically located between the cerebrum and the brainstem. The complex neural circuits associated with the hypothalamus have reciprocal and widespread connections with these regions. The hypothalamus derives its major input from the nonspecific reticular pathways and little, if any, from the specific lemniscal pathways. The structures projecting to, and receiving input from, the hypothalamus include the brainstem reticular formation, limbic lobe (including hippocampus and amygdala), thalamus, and olfactory pathways. The major pathway of the hypothalamus is the medial forebrain bundle. This is an intricate complex of short, multisynaptic, multineuronal chains extending from the limbic system to the lateral hypothalamus and the paramedian tegmentum of the midbrain.

Input (*see* Fig. 21.3)

The *input to the hypothalamus* is conveyed via (1) ascending pathways from the spinal cord, brainstem tegmentum, and periaqueductal gray matter (*see* **Fig. 20.5**), (2) descending fibers from the forebrain, and (3) the blood vascular system. The neurons of the hypothalamus respond to a variety of messengers. They contain receptor sites for (1) such neurotransmitters as acetylcholine, norepinephrine, dopamine, serotonin, and numerous neuropeptides and (2) such agents as sex steroid hormones, thyroxin, and hormones released by the adenohypophysis.

1. The *ascending pathways from (a) the spinal cord are spinohypothalamic* pain fibers and from (b) the *brainstem* mainly are fibers of the *mammillary peduncle* from the dorsal and ventral tegmental nuclei (*see* **Fig. 13.14**), fibers of the *dorsal longitudinal fasciculus* from the periaqueductal gray matter, fibers of the *medial forebrain bundle* from the midbrain tegmentum, and catecholamine pathways from several brainstem nuclei, including some noradrenergic fibers from the locus ceruleus that partially ascend with the central tegmental tract (Chap. 22).
2. The *descending fibers from the forebrain* include the following (*see* **Fig. 21.3**):
   a. Fibers of the fornix originating in the hippocampus and the septal nuclei of the limbic system. The hippocampus is a significant channel for afferent and neocortical input to the hypothalamus.
   b. Fibers originating in the cortex of the uncus and amygdala. These project via the stria terminalis and ventral amygdalofugal pathway to the hypothalamus. The primary olfactory cortex projects via fibers of the medial forebrain bundle (Chap. 22). Thus. the olfactory system has a direct route to the hypothalamus.
   c. Fibers arising from melanopsin-containing retinal ganglion cells terminate in the suprachiasmatic nucleus.
   d. The orbitofrontal cortex and septal nuclei, the source of fibers of the medial forebrain bundle.
   e. the dorsomedial and midline nuclei of the thalamus, which project to the hypothalamus and amygdala.
3. The *blood vascular system* conveys influences to which the hypothalamus might respond. These include hormones, temperature of the blood and osmolality of the blood, plasma.

Output (*see* Fig. 21.4)

The *output from the hypothalamus* is conveyed via (1) ascending fibers to the forebrain, (2) descending fibers to the brainstem and spinal cord, and (3) fibers and blood vessels to the hypophysis (endocrine effector projections).

1. The *ascending fibers from the hypothalamus to the forebrain* include those projecting to the anterior and dorsomedial thalamic nuclei, septal nuclei, and septal (subcallosal) area.
2. The *descending fibers* to the midbrain and pons project to the dorsal and ventral tegmental nuclei, superior central nucleus (a raphe nucleus), and the periaqueductal gray matter. The dorsal vagal nucleus and adjacent nuclei in the medulla also receive projections from the hypothalamus. The descending tracts from the hypothalamus include the dorsal longitudinal fasciculus, medial forebrain bundle, and mammillotegmental fasciculus.
3. The influences from the *hypothalamus to the hypophysis* are conveyed via the hypophyseal portal system to the adenohypophysis and via the supraopticohypophyseal tract to the neural lobe (see below).

These projections to and from the hypothalamus are involved with the functional activities of the autonomic nervous system (Chap. 20), limbic system (Chap. 22), and endocrine system via the neurohumoral reflexes.

NEUROHUMORAL REFLEXES

The hypothalamus is integrated into distinct neurohumoral reflexes in which two separate

fiber pathways extend from the hypothalamus to the hypophysis. The neurons of these pathways are involved with both neurally and humorally conveyed stimuli.

Tuberohypophyseal Tract

The tuberohypophyseal tract projects from the hypothalamic nuclei located in the hypophysiotropic area in the medial basal hypothalamus (includes the tuber cinereum) and terminates in the infundibular stem (*see* **Fig. 21.2**). The neurons of this tract elaborate and convey hypophysiotropins (hypothalamic-releasing hormones) to the capillary loops of the hypophyseal portal system and, via this vascular system, to the adenohypophysis of the pituitary gland. These hypophysiotropins are peptides that exert their influences upon the release (or nonrelease) of various hypophyseal hormones into the systemic circulation. The neurons of the tuberohypophyseal tract constitute the parvocellular neurosecretory system, so called because its neurons have axons with small diameters. In a sense, the portal system into which the hypophysiotropins are released is actually a huge synaptic cleft; the portal system bridges the gap between the presynaptic tuberohypophyseal tract and the postsynaptic cells of the anterior lobes. In another context, the portal veins are a "final common pathway."

Releasing Hormones

1. *Gonadotropin-releasing hormone* (GnRH) that regulates the release of follicle stimulating hormone (FSH, follitropin) and luteinizing hormone (LH, lutropin) from the hypophysis.
2. *Thyrotropic hormone-releasing hormone* (TRH) that regulates the release of thyrotropin (thyroid-stimulating hormone, TSH) and prolactin from the hypophysis.
3. *Corticotropin-releasing hormone* (CRH) that regulates the release of adrenocorticotropin (adrenocorticotropic hormone, ACTH), *cortisol,* and β-lipotropin from the hypophysis. (β-lipotropin hormone is a precursor of endorphins and ACTH.)
4. *Growth hormone-releasing hormone* (GRH or GHRH) that regulates the release of growth hormone (somatotropin) from the hypophysis.
5. *Prolactin-releasing factor* (PRF) is the putative releasing hormone that regulates the release of prolactin (lactogenic hormone, mammotropic hormone) from the hypophysis.
6. *Melanocyte-stimulating hormone-releasing factor* (MRF) is the putative releasing hormone that stimulates the release of melanocyte stimulating hormone and β-endorphin from the hypophysis. In man, melanocyte-stimulating hormone (MSH) stimulates the formation of melanin pigment and its dispersion in melanocytes.

Inhibiting Hormones

1. *Growth hormone release-inhibiting hormone* (GIH, GHRIH) also called *somatostatin* (SS) or *somatotropin release-inhibiting hormone* (SRIH) acts to inhibit the release of growth hormone and thyrotropin from the hypophysis.
2. *Prolactin release-inhibiting hormone* (PIH) or *dopamine* (DA) acts to inhibit the release of prolactin from the hypophysis.
3. *Melanocyte-stimulating hormone release-inhibiting factor* (MIF) acts to inhibit the release of melanocyte-stimulating hormone.

A complex series of feedback systems to the hypothalamus and to the hypophysis have a significant role in regulating and controlling the secretory activity of these hormones. They comprise (1) a *long feedback loop*, in which the hypothalamus monitors hormones synthesized by the peripheral target organs (e.g., thyroxine released by the thyroid gland is fed back via the bloodstream to be monitored by the hypothalamus), (2) a *short feedback loop*, in which each tropic hormone of the pituitary gland is fed back to, and monitored by, the hypothalamus, (3) an even shorter feedback loop, in which the releasing hormones feed back to and are monitored by the hypothalamus, and (4) a feedback

loop in which each tropic hormone within the tissues is fed back to the hypophysis to influence and regulate the release of the same tropic hormone (e.g., growth hormone).

All of the hypophysiotropic peptides originally found in the hypothalamus are now known to be ubiquitous in the brain, although located in certain neurons. They are also found in the tissues of the gastrointestinal tract. The vasoactive intestinal peptide (VIP), which was originally identified in the gut, is also found in the central nervous system (CNS). The role of hypophysiotropic peptides in these organs has not, as yet, been resolved. In addition, receptors for these substances have been found in many peripheral organs, but it is not clear what role these peptides play.

The peptides, once released into the synaptic space, are not recovered by a neuronal uptake mechanism similar to that for norepinephrine. Apparently, all of the peptides available to presynaptic release sites are totally dependent on ribosomal synthesis in the cell body and are transported by axoplasmic flow to the synaptic terminals. The neuropeptides within neurons of the CNS coexist with the classical neurotransmitters. When released in the synaptic cleft, they act to alter the excitability of the postsynaptic membrane.

Supraopticohypophyseal Tract

The supraopticohypophyseal tract (*see* **Fig. 21.2**), made up of about 100,000 unmyelinated fibers, extends from the supraoptic and paraventricular nuclei to the capillary bed of the neurohypophysis (posterior lobe). The fibers convey, via axoplasmic transport, *antidiuretic hormone* (ADH, vasopressin), which is involved with the homeostatic role of conserving water regulating the tonicity of body fluids, and *oxytocin*, which has a role in stimulating the contraction of smooth muscles of the uterus and promoting the ejecting of milk from the lactating mammary glands by stimulating contractions of its myoepithelial cells.

The neurons of this tract constitute the magnocellular neurosecretory system with its large-diameter axons. They synthesize the precursors (prohormones) of the hormones that are conveyed by axoplasmic flow to the neural lobe. Oxytocin and ADH are synthesized in the cell bodies in different neurons. Both types of neurons are located in both the supraoptic nucleus and paraventricular nucleus. With the appropriate stimulus, an action potential is conveyed down the axon. This triggers the inflow of calcium followed by the release of the ADH or oxytocin at this neurovascular synapse with the fenestrated capillary wall into the systematic circulation.

INFLUENCES ON THE AUTONOMIC NERVOUS SYSTEM

The hypothalamus is the chief *subcortical* center regulating all kinds of visceral activities and some somatic functions; it acts primarily as a modulator of autonomic centers in the brainstem and spinal cord (Chap. 20).

The *anterior hypothalamus* (preoptic and supraoptic regions) has an excitatory parasympathetic (or inhibitory to sympathetic activity) role. The stimulation of this region can produce a decrease in the rate of the heartbeat, a decrease in blood pressure, dilatation of the cutaneous blood vessels, an increase in motility, peristalsis, and secretion in the gastrointestinal tract, constriction of the pupil, and increased sweating. Activity in this region produces a parasympathetic (vagal) tone and such somatic responses as panting. Lesions in this area can result in the production of sympathetic effects.

The *posterior hypothalamus* has an excitatory sympathetic role. Activation of this region can produce an increase in the rate of the heartbeat, an increase in blood pressure, constriction of cutaneous blood vessels, a decrease in motility, peristalsis, and secretion in the gastrointestinal tract, dilatation of the pupil, and erection of hair. Activity in this region produces a sympathetic tone and such somatic responses as shivering, running, and struggling.

The *descending projections* from the hypothalamus are involved with regulating a variety of bodily functions through its influences on the

autonomic nervous system (Chap. 20). Some of its influences are involved with certain somatic functions. The latter include a role in (1) shivering produced by the activity of voluntary muscles and (2) the activities of the voluntary palatal and pharyngeal muscles associated with the ingestion of food (the latter are innervated by the nucleus ambiguus, a brainstem nucleus).

The descending fibers influencing the autonomic nervous system include the (1) dorsal longitudinal fasciculus (DLF) in the medial brainstem tegmentum and (2) fibers in the dorsolateral tegmentum. The DLF extends caudally in the medulla and innervates the superior and inferior salivatory nuclei and the dorsal motor nucleus of the vagus nerve; all are the source of parasympathetic outflow (Chap. 20). Some fibers terminate in the nucleus solitarius, a visceral sensory nucleus (Chap. 14). These fibers can constitute a *reflected feedback pathway* modulating visceral sensory input. The fibers in the dorsolateral tegmentum extend throughout the length of the spinal cord. Some of their fibers can terminate in the parasympathetic nuclei of the brainstem and they also terminate (1) in the lateral intermediate zone of T1 to L2, the location of the outflow of the sympathetic system, and (2) S2 to S4, the location of the outflow of the parasympathetic system.

A lesion in the dorsolateral tegmentum of the medulla can interrupt the descending sympathetic fibers and result in Horner's syndrome (Chap. 12). This can be the consequence of an obstruction of the posterior inferior cerebellar artery (PICA) (Chap. 4). The symptoms include miosis of the pupil, ptosis of the eyelid, decreased sweating, and increased warmth and redness on the side of the face; all occur on the ipsilateral side, indicating that these fibers descend without crossing.

TEMPERATURE REGULATION

The hypothalamus has an essential role in body temperature; it regulates the balance between heat production and heat loss. More specifically, the hypothalamus has thermal receptor neurons, which monitor the temperature of the blood. This "thermostat" regulates the heat-producing and heat-conserving control systems. In effect, the continuous fine adjustments necessary for maintaining a constant normal body temperature depend on the hypothalamus.

The anterior hypothalamus acts to prevent a rise in body temperature. It activates those processes that favor heat loss, including vasodilatation of cutaneous blood vessels, sweating (evaporation of water for cooling), and panting. Destruction of this "heat-dissipating region" can produce a highly elevated body temperature (hyperthermia).

The posterior hypothalamus contains a region that triggers those activities concerned with heat production and heat conservation. These include the metabolic heat-producing systems (thermogenesis by the oxidation of glucose), vasoconstriction (especially of cutaneous blood vessels), erection of hair (goose pimples), and shivering. The malfunctioning of this region can produce a cold-blooded mammal that cannot sustain a uniform body temperature.

Pyrogenic substances, produced in some diseases, affect the hypothalamus, causing a fever known as *neurogenic hyperthermia*.

REGULATION OF WATER BALANCE

The hypothalamus has significant roles in fluid balance by regulating both the intake (by drinking) and output (through kidneys and sweat glands) of water. Evidence indicates that a "drinking" or "thirst" center is located in the lateral hypothalamus and a "thirst satiety" center in the medial hypothalamus. The *osmoreceptor neurons* in these hypothalamic centers respond to the osmolality (electrolyte composition) of the blood passing through these nuclei. They set off events that stimulate or inhibit water intake. Other factors such as dryness of the oral mucosa from decreased salivary flow also influence intake of water. A salt appetite is generated by the effect of the electrolyte composition of the blood on the gustatory system.

The hypothalamus has a crucial role in the conservation and loss of body water through the regulation of urine flow in the kidneys by ADH, which is produced by the neurons of the supraoptic and paraventricular nuclei of the hypothalamus. ADH (vasopressin) is synthesized by the neurons in these nuclei and carried by axoplasmic transport in the supraopticohypophyseal tract to the neurohypophysis, where it is stored or released into the systemic blood circulation. The ADH acts upon the kidney (distal convoluted and collecting tubules) to increase the reabsorption of water from the dilute glomerular filtrate in the tubules back into the bloodstream, thus concentrating the urine. Water is thereby conserved and is not excreted in the urine. Increases in osmolality in blood flowing through the hypothalamus stimulate the release of ADH; this results in antidiuresis and conservation of water. Decreases in osmolality inhibit the release of ADH; this results in diuresis and excretion of water in urine. Other factors can have a role; vascular receptors monitoring blood volume or flow in the body project input to the hypothalamus, in this way influencing the release of ADH.

A deficiency in the formation and release of ADH can result in *diabetes insipidus* (increased excretion of water without increase in sugar), in which as much as 10–12 L of urine may be excreted per day.

Following an injury of the infundibular stem and the axons of its neurons, diabetes insipidus may result. This may be temporary, because the axons regenerate and a new functional neurohypophysis is established.

FOOD INTAKE AND ENERGY BALANCE

The hypothalamic region involved with feeding responses has been called the "appestat," with the ventral medial hypothalamic nucleus called the "satiety center" and the lateral hypothalamic nucleus called the "hunger" or "feeding" center. Stimulation of the ventral median nucleus inhibits the animal's urge to eat. Destruction of the pair of nuclei produces an animal exhibiting decreased physical activity and a voracious appetite (not true hunger) with a twofold to threefold increase in food intake. The animal becomes obese. Stimulation of the lateral hypothalamic nucleus induces the animal to eat, whereas its destruction produces an animal that refuses to eat until severe emaciation from starvation ensues.

Two theories have been proposed to explain how these centers are influenced. According to the *glucostat hypothesis*, hypothalamic neurons respond to blood glucose levels. According to the *thermostat hypothesis*, blood temperature is the causative factor, with an increase resulting from the specific dynamic action of ingested blood and with a decrease resulting from dissipation of heat through the skin.

EXPRESSIONS OF EMOTION AND BEHAVIOR

The behavioral patterns associated with emotional experiences are of two general types: (1) subjective "feelings" and (2) objective physical expressions. The subjective aspects of emotion, from depression to euphoria, are more intimately bound up with the cerebral cortex. Many of the objective physical expressions are largely mediated through the hypothalamus and are recognizable as the enhanced activity of the autonomic nervous system. They include alterations in heartbeat (palpitations) and blood pressure, blushing and pallor of the face, dryness of the mouth, clammy hands, dilatation of the pupil (glassy eye), cold sweat, tears of happiness or sadness, and changes in the concentration of blood sugar. Stimulation of the hypothalamus in man is said to evoke changes in blood pressure and rate of heartbeat without any psychic manifestations.

Sexual Expressions

The sympathetic and parasympathetic systems are integrated in sexual and reproductive activities. Commencing with sexual arousal elicited from either psychologic or genital stim-

ulation, the subsequent phases are essentially similar in both male and female. In the next phase, the engorgement of the erectile tissue resulting in the erection of the clitoris and penis is a response to parasympathetic stimulation (nervus erigentes of S3 and S4). Loss of parasympathetic activity, as in diabetic neuropathy, results in impotency in the male (failure of erection and ejaculation). In the female, the parasympathetic fibers stimulate the secretions from the cervical glands to further moisten the vagina and engorge the labia minora. Stimulation by sympathetic fibers produces peristaltic waves that propel semen along the ductus deferens and contractions that discharge emission secretions from the seminal vesicles and prostate gland to form the substance of the ejaculate. The phase of ejaculation through and out of the urethra involves the coordinated activity of the parasympathetic fibers and somatic motoneurons (pudendal nerves S2–S4). During the orgasm, the motoneurons evoke the spasmodic contraction of the bulbocavernous, ischiocavernous, and pelvic floor voluntary muscles that eject the ejaculate from the penis. Weakness of erection or premature ejaculation can occur as the consequence of overactivity of the sympathetic system. Often, this has an emotional basis. Depression of sympathetic activity, following treatment with certain drugs, could result in impaired ability to ejaculate.

"Pleasure Centers" and "Punishing Centers"

The hypothalamus is very closely linked to the limbic system and, not uncommonly, is considered part of it. Stimulation of some parts of the hypothalamus elicits expressions of pleasure or of punishment (see Chap. 22).

Responses to Intense Stress and Trauma

The response of the brain to profound crises involving intense stress and trauma is to mobilize the resources that act to protect the organism. This includes activating the neural circuits involved with the "fight, fright and flight" activities (Chap. 20). Among these are (1) the release of catecholamines for the initial preparation for the emergency by the neurons of the locus ceruleus with their widespread distribution (Chap. 15), (2) the release of pain-blunting endorphins and enkephalins by the hypothalamus and other neural complexes (Chap. 9), and (3) the release of the stress-response hormones by the hypothalamus and pituitary gland, namely corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol by the adrenal gland. Cortisol is an adrenal stress hormone that mobilizes energy and inhibits the immune system.

CIRCADIAN RHYTHMS

Cues of environmental time such as the daily light/dark cycle entrain (synchronize) physiological and behavioral activities to a 24–hour day/night cycle—the circadian rhythm (circa, about + diem, day). An endogenous oscillator called the internal circadian clock (pacemaker) located in the suprachiasmatic nucleus generates and controls the circadian rhythm. This clock allows organisms to anticipate rhythmic changes in the environment and alter their physiological state, thus providing them with an adaptive advantage. Although the cycle persists in the absence of environmental cues, its duration is altered by external signals called zeitgebers (time givers). Zeitgebers reset the clock so that internal time matches local time (entrainment). For example, light is a powerful timing cue, which is linked to the active phase of the circadian cycle in some animals (diurnal) and to the inactive phase in others (nocturnal). Most adult humans and diurnal animals sleep at night when it is dark, whereas nocturnal animals sleep mostly during the day when it is light. Circadian rhythms also are manifested by fluctuations in body temperature, metabolic rate, urine production, and hormone secretions. The ubiquitous seasonal rhythms of mammals, including the annual migrations of caribou, the winter hibernation of marmots and bears, and the reproductive cycles of rutting elk in the autumn, resulting in fauns being born in the spring, might also be regulated by circadian clocks.

The Suprachiasmatic Nucleus

In vertebrates, the circadian clock is located in the *suprachiasmatic nucleus* (SCN). The SCN, located in the anterior hypothalamus just above the optic chiasma (*see* **Fig. 21.1**) is the internal master clock of the *circadian timing system*, a system of neural circuits with the primary role of adapting to the environmental solar rhythms of light/dark, called the sleep–wake cycle. The rhythm that is generated by the SCN is called the endogenous "free-running" rhythm. It is approximately but not exactly 24 hours and varies for different species. The endogenous rhythm is entrained to environmental light–dark cycles.

An endogenous biological clock oscillates in the fetus. Apparently, this clock is entrained by circadian signals from the mother and prepares the developing fetus to adapt more readily to adjust to life following birth. It should be noted that circadian rhythms tend to be disrupted in people who are blind.

Light that stimulates the retina activates a recently discovered subset of light-detecting retinal ganglion neurons whose dendrites contain the photopigment *melanopsin*. These widely dispersed neurons, constituting about 2% of retinal ganglion cells, have tortuous broad overlapping dendritic fields optimally arranged to detect low levels of light. Following stimulation, this population fires continuously without adaptation for at least 20 minutes, in contrast to ganglion cells that receive input from rods and cones. Activation of the melanopsin-containing ganglion cells, which project directly to the SCN via the retinohypothalamic tract, entrains mammalian circadian rhythms to environmental time. As indicated in Chapter 19, these cells also have been implicated in circuitry to the pretectum mediating the pupillary light reflex and to the superior colliculus controlling eye movements.

Sleep–Wake Cycle

A normal day is divided into waking and sleeping phases. Sleep typically occurs in repetitive cycles of different stages as elucidated by direct observation, electrical recordings of brain waves (electroencephalogram or EEG), recordings of muscle activity (electromyogam), and recordings of eye movement (electro-oculogram). Stage 1 is a transitional light sleep that lasts for but a few minutes during which muscles relax as one drifts in and out of wakefulness. The body temperature is lowered, the eyes make slow rolling movements, and the subject sees fragmentary images. The frequency of the EEG diminishes and the amplitude slightly increases. This is the lightest level of sleep from which one can be easily aroused. Stage 2 sleep is slightly deeper and lasts for about 5–15 minutes. During this stage, the heart and respiratory rates decrease and eye movements almost cease. The frequency of the EEG diminishes further and the amplitude increases. The pattern is interspersed with high-frequency spikes referred to as sleep spindles. Stage 3 sleep is regarded as moderately deep. Body movements are absent and the EEG is characterized by low-frequency, higher-amplitude waves and a reduction in spindle activity. Stage 4 is the deepest level during which it is most difficult to awaken a sleeping subject. The muscles are greatly relaxed and blood pressure, heart rate, and breathing are at their lowest. The pupils are constricted (miosis). The EEG is characterized by low-frequency high-amplitude waves and its conformation conveys the designation slow-wave sleep. This phase lasts about 20–40 minutes. Following stage 4, the EEG pattern reverts to a pattern resembling the waking-state**,** high-frequency, low-amplitude. However, this phase is characterized by rapid eye movements (REM) and this aspect is strikingly different from the other stages collectively called non-REM sleep. The period following REM sleep is accompanied by a complete inhibition of tone in other skeletal muscles. The sequence of non-REM and REM phases normally has four to six cycles per night.

During REM sleep, electrical activity of the brain is unusually high, somewhat resembling that of wakefulness. This REM stage is called paradoxical sleep, during which most dreams replete with visual imagery occur and can be

readily retrieved. Heart rate and blood pressure rises along with EEG activity. Homeostatic mechanisms are attenuated. Respiration is relatively unresponsive to changes in CO_2 and responses to heat and cold are greatly reduced. In REM sleep, the rate and depth of breathing increases, but the muscles are greatly relaxed, more so than during the deepest levels of non-REM sleep. Most dreaming, night terrors, and sleep walking occurs during stage 4 and REM sleep. REM sleep normally follows immediately after each stage 4 non-REM period, but can occur occasionally after any one of the four stages. There is a general reduction of the non-REM periods as the night progresses, especially in stages 3 and 4, and an increase in the REM periods toward the end of a normal sleep. About half of the night's sleep occurs during the third and longest REM cycles, which can last 40–50 minutes. Occasionally, each REM cycle can be followed by at least 30 minutes of non-REM sleep before a new cycle begins. The start of the non-REM phase to the end of the REM phase averages about 90–110 minutes.

Melatonin. The neurohormone melatonin, synthesized in the pineal gland from tryptophan, has been implicated as a modulator of the sleep–wake cycle and is promoted as a safe natural sleeping pill. The pineal, one of the circumventricular organs described in the next section, is a highly vascular neuroendocrine gland located in the caudal epithalamus (*see* **Figs. 13.3 and 21.5**). Its pinealocytes (parenchymal cells) have processes that extend to perivascular spaces that surround fenestrated capillaries. The suprachiasmatic nucleus, which receives retinal input, regulates the release of melatonin into the pineal capillaries and the vascular circulation. In turn, melatonin modulates brainstem circuits associated with the sleep–wake cycle.

When given to rats during the daytime, melatonin stimulates wakefulness. On the other hand, it has a substantial sleep-inducing (hypnotic) effect in birds. As yet, human studies have not demonstrated consistent sleep-inducing effects mediated by melatonin. Some recent observations do indicate that it can facilitate sleep onset in elderly humans who are deficient in melatonin. It might be of value in overcoming jet lag.

Both sleep and wakefulness are activities generated by the interplay of neuronal populations involving circuitry within the *basal forebrain and brainstem reticular formation* (Chap 22). The neurons of these sleep-control circuits are linked and coordinated by many neurotransmitters and the suprachiasmatic nucleus. The following are some components of these circuits that are included because of their association with certain features of the EEG and behavioral expressions.

Neurons within the basal nucleus of Meynert (*see* **Fig. 22.2**) located in the basal forebrain have a modulatory role during arousal and selective attention. Neurons, called waking-up neurons located mainly in the brainstem reticular formation, actively fire both during the wakeful state and in REM sleep. The firing of neurons in the pontine reticular nuclei during REM sleep concurrently activates a circuit that elicits REMs and another circuit that inhibits lower motoneurons of the spinal cord, which prevents movements of the limbs (running during a dream). The latter occurs because the upper motoneurons stimulate spinal interneurons that release the inhibitory transmitter glycine at their synapses with lower motoneurons.

THE CIRCUMVENTRICULAR ORGANS

Adjacent to the median ventricular cavities (third ventricle, cerebral aqueduct, and fourth ventricle) are specialized areas called *circumventricular organs*. These include (1) the median eminence of the tuber cinereum, the neurohypophysis, and the pineal body, which are sites of neuroendocrine activity, and (2) the organum vasculosum of the lamina terminalis, subfornical organ, subcommissural organ, and the area postrema (*see* **Fig. 21.5**), which are chemoreceptive areas whose functional roles are not fully understood. The common vascu-

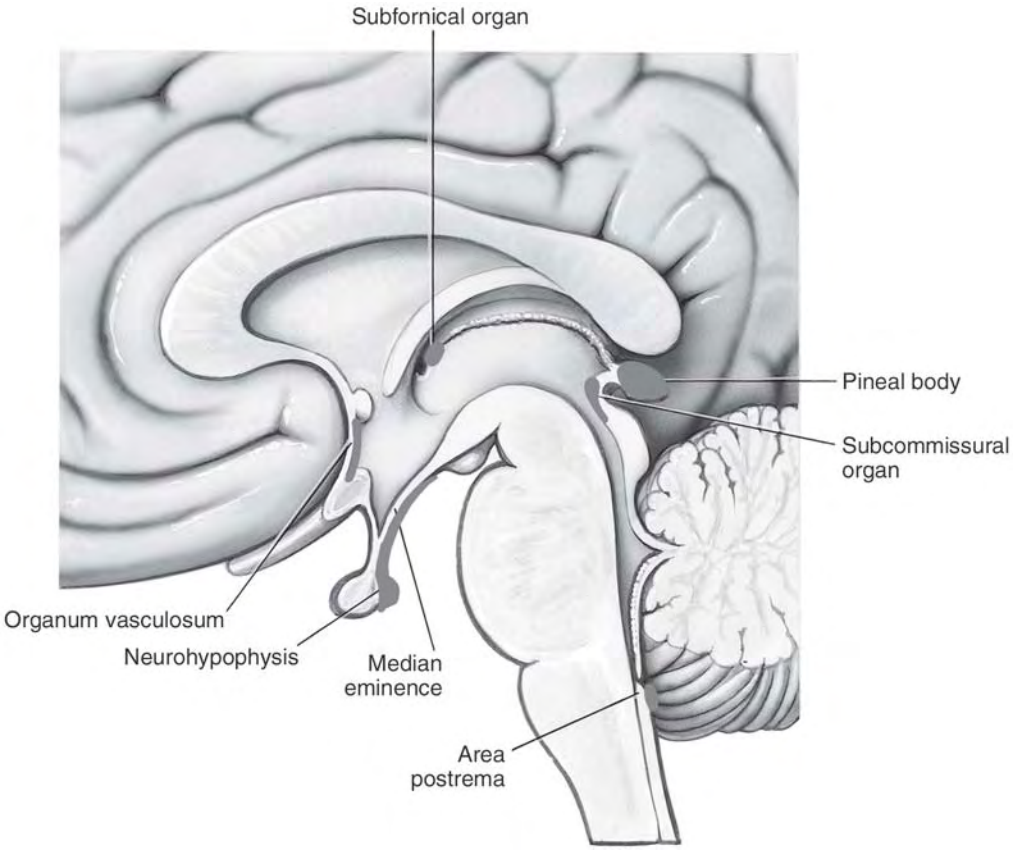


Figure 21.5: Midsagittal view of the brain illustrating the location of the circumventricular organs.

lar, ependymal, and neural organization of these structures differs from that found in typical brain tissue. They are referred to as "being in the brain but not of it" and as leaky areas, primarily because they lack a blood–brain barrier. All circumventricular organs are unpaired and located along the ventricular surface near the midline except for the paired area postrema of the medulla. These leaky areas are isolated from the brain by a lining of specialized ependymal cells, called tanacytes, that separate these organs from the ventricles. The tanacytes are linked to each other by tight junctions and, thus, prevent the free exchange between the circumventricular organs and the cerebrospinal fluid.

Median Eminence of the Tuber Cinereum

The *median eminence* of the *tuber cinereum* is that portion of the floor of the hypothalamus where the releasing and inhibiting hormones are released from the axon terminal into the capillary loops of the hypophyseal portal system. In essence, it is the site of the neurovascular link between the CNS and the adenohypophysis.

Neurohypophysis

As previously noted, the *neurohypophysis* is the site for the storage and release of vasopressin and oxytocin, which are synthesized in the supraoptic and paraventricular nuclei. The nerve terminals of the supraopticohypophyseal

tract containing these neurohormones are intermingled among cells called pituicytes, which are modified glial cells.

Organum Vasculosum of the Lamina Terminalis and Subfornical Organ

The *organum vasculosum* of the *lamina terminalis* (*supraoptic crest* and "*prechiasmatic gland*") is a highly vascular region of the lamina terminalis. Its loops of fenestrated capillaries are surrounded by wide, fluid-filled perivascular spaces.

The subfornical organ (*intercolumnar tubercle*) is an elevation located between the diverging columns of the fornix at the level of the interventricular foramina of Monro. It is partially covered by the choroid plexus. Its sinusoids and glomerular loops are supplied by adjacent blood vessels.

These two organs have nerve endings synapsing with their neurons. In addition, the messenger angiotensin II, the production of which is enhanced by a reduction in blood volume, binds to receptor sites of the neurons of these organs. The neurons have axons that project to the supraoptic and paraventricular nuclei of the hypothalamus. The interaction within these organs seems to provide the feedback information involved with the hypothalamic control of the posterior lobe of the hypophysis. This includes roles in drinking behavior (osmoregulation), release of antidiuretic hormone, and the physiological control of body fluid balance.

Subcommissural Organ

The *subcommissural organ* is located in the roof of the cerebral aqueduct just rostral and ventral to the posterior commissure. It is composed of specialized ependymal cells and glial cells in a capillary bed of nonfenestrated endothelium. The secretory ependymal cells release a neutral mucopolysaccharide compound product directly into the ventricular fluid. It condenses to form Reissner's fiber, which extends through the cerebral aqueduct, fourth ventricle, and central canal of the spinal cord to coccygeal levels. Its function is not known.

Area Postrema

The *area postrema* consists of paired small, rounded eminences that occupy the wall of the caudal end, or obex, of the fourth ventricle, where it meets the central canal (*see* **Fig. 13.3**). It is composed of modified neurons, astrocytelike cells, and rich overlapping arterial and sinusoidal network. The terminals in the vicinity of the area postrema are of axons originating in the vagus nerve, nucleus solitarius, and the spinal cord. These endings contain oxytocin, vasopressin and other peptides not found within the area postrema. It is regarded as an emetic chemoreceptor sensitive to substances that are unusual constituents such as toxins circulating in the blood. The area postrema acts as a trigger zone that evokes the vomiting reflex in response to a host of emetic agents including apomorphine and digitalis glycosides.

SUGGESTED READINGS

Berson DM. Strange vision: ganglion cells as circadian photoreceptors. *Trends Neurosci.* 2003;26: 314–320.

Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. *Science* 2002;295:1070–1073.

Burbach JP, Luckman SM, Murphy D, Gainer H. Gene regulation in the magnocellular hypothalamo-neurohypophysial system. *Physiol. Rev.* 2001;81:1197–1267.

Carpenter DO. Central nervous system mechanisms in deglutition and emesis. In: Schultz SG, ed. *Handbook of Physiology. Section 6: The Gastrointestinal System.* Bethesda, MD: American Physiological Society; 1989:685–714.

Conn PM, Freeman ME. *Neuroendocrinology in Physiology and Medicine.* Totowa, NJ: Humana; 2000.

Hall JC. Cryptochromes: sensory reception, transduction, and clock functions subserving circadian systems. *Curr. Opin. Neurobiol.* 2000;10: 456–466.

Harmer SL, Panda S, Kay SA. Molecular bases of circadian rhythms. *Annu. Rev. Cell. Dev. Biol.* 2001;17:215–253.

King DP, Takahashi JS. Molecular genetics of circadian rhythms in mammals. *Annu. Rev. Neurosci.* 2000;23:713–742.

Klein DC, Moore RY, Reppert SM. *Suprachiamatic Nucleus: The Mind's Clock.* New York: Oxford University Press; 1991.

Korf H-W, Usadel K-H. *Neuroendocrinology: Retrospect and Perspectives.* New York: Springer-Verlag; 1997.

Laemle LK, Hori N, Strominger NL, Tan Y, Carpenter DO. Physiological and anatomical properties of the suprachiasmatic nucleus of an anophthalmic mouse. *Brain Res.* 2002;953:73–81.

Lowrey PL, Takahashi JS. Genetics of the mammalian circadian system: photic entrainment, circadian pacemaker mechanisms, and posttranslational regulation. *Annu. Rev. Genet.* 2000;34: 533–562.

Lucas RJ, Hattar S, Takao M, Berson DM, Foster RG, Yau KW. Diminished pupillary light reflex at high irradiances in melanopsin-knockout mice. *Science* 2003;299:245–247.

Miller AD, Ruggiero DA. Emetic reflex arc revealed by expression of the immediate-early gene c-fox in the cat. *J. Neurosci.* 1994;14:871–888.

Nauta WJH, Haymaker W. Hypothalamic nuclei and fiber connections. In: Haymaker W, Anderson EM, Nauta WJH, eds. *The Hypothalamus.* Springfield, IL: Charles C Thomas; 1969; 136–209.

Reppert SM, Weaver DR. Coordination of circadian timing in mammals. *Nature.* 2002;418:935–941.

Sawchenko PE. Toward a new neurobiology of energy balance, appetite, and obesity: the anatomists weigh in. *J. Comp. Neurol.* 1998;402: 435–441.

Sawchenko PE, Li HY, Ericsson A. Circuits and mechanisms governing hypothalamic responses to stress: a tale of two paradigms. *Prog. Brain Res.* 2000;122:61–78.

Silverman AJ, Zimmerman EA. Magnocellular neurosecretory system. *Annu. Rev. Neurosci.* 1983;6:357–380.

Swanson LW, Sawchenko PE. Hypothalamic integration: organization of the paraventricular and supraoptic nuclei. *Annu. Rev. Neurosci.* 1983;6:269–324.

Williams RH, Larsen PR. *Williams textbook of endocrinology.* 10th ed. Philadelphia, PA: Saunders; 2003.

22
The Reticular Formation and the Limbic System

Reticular Formation
Limbic System
Role of the Limbic System

The reticular formation (RF) is a seemingly diffuse, but actually highly organized, network of neurons distributed through the tegmental core of the brainstem. The RF extends rostrally as the intralaminar nuclei of the thalamus and caudally as the gray matter in the vicinity of the central canal of the spinal cord. The RF receives the summation of sensory information that flows into the spinal cord and brainstem via the peripheral nerves. These inputs are significant in influencing the level of arousal (i.e., the responsive tone of conscious awareness and physical performance). The RF contains assemblies of interacting neurons that integrate reflexes and basic stereotyped action patterns mediated by cranial nerve input. The basic motor responses range from facial nerve-innervated muscle responses to mechanisms of eating, drinking, and breathing. They are centrally coordinated and assembled as highly complex behaviors under voluntary control by higher cerebral motor circuits, including those of the limbic system. The precise and subtle patterns of motor behaviors mediated by cranial nerves involve the organized circuitry of the brainstem RF.

The limbic system (LS) is involved with emotional behaviors, endocrine and autonomic regulation, and mechanisms of memory formation. The emotional behaviors comprise activities exhibited during satiety, quiescence, prayer, aggression, fear, rage, and sexual activity. Anatomically, the limbic system is an interconnected neuronal network of neocortical areas and subcortical structures. Neo- and mesocortical areas include the anterior cingulate gyrus (area 24) and orbitofrontal and medial prefrontal cortex (areas 10 and 11). The subcortical centers include the nuclei of the septal area, and the nucleus accumbens (portion of the ventral striatum). Substantive information is integrated within the thalamus and *amygdala*. In turn, the amygdala projects its outputs to the thalamus, hypothalamus, and the brainstem, where they activate the *emotional state* through the endocrine system and the autonomic nervous system (Chaps. 20 and 21). The networks of the limbic system are linked together by bidirectional reciprocal pathways.

Collectively, the limbic system and the reticular formation are neural constructs that have at least two things in common: (1) Anatomically, they both are substantially heteromorphic systems and (2) their actions are woven into the fabric of emotional and behavioral expressions in a way that makes it difficult to define precisely their individual roles in the totality of limbic action.

RETICULAR FORMATION

Anatomy

The RF extends throughout the length of the brainstem tegmentum. Microscopically, the RF appears as gray matter commingled with fascicles of ascending and descending axons and dendritic arbors imparting the appearance of a woven network (Nauta and Fiertig, 1986). The RF occupies the space in the tegmentum not taken up by motor nuclei, nuclei of the sen-

sory pathways (e.g., trigeminal and superior olivary nuclei), cerebellar relay nuclei (e.g., inferior olivary complex) and circumscribed fiber tracts (e.g., medial lemniscus and medial, longitudinal fasciculus). The RF in conjunction with the nuclei of the raphe (*see* **Fig. 13.6**) and the periaqueductal gray (*see* **Fig. 13.15**) extends *rostrally* into thalamic areas having visceral functions, consisting in part of the periventricular gray adjacent to the third ventricle, the parafascicular and central median nuclei of the intralaminar thalamic group (*see* **Fig. 23.1 and Table 23.1**), and the *zona incerta* and other nuclei near the subthalamic nucleus (*see* **Fig. 24.3**).

The neurons of the brainstem RF have extensively branched dendritic trees oriented in a transverse plane as "segments" and long branching axons that project both rostrally and caudally (*see* **Fig. 22.1**). These axons form a widespread network connecting with neurons of the hypothalamus, thalamus, cerebrum (including cerebral cortex), cerebellum, and spinal cord.

Ascending influences from the spinal cord are processed and conveyed to and within the RF by ascending reticular projections such as spinoreticular fibers (Chap. 9) and the *central tegmental tract* (Chap. 13) and by descending influences from the forebrain by direct and indirect downward projections from the cerebral cortex, basal ganglia, and forebrain limbic system.

The circuitry essential to various behavioral states, such as the sleep–wake cycle, is known as the ascending reticular activating system (ARAS). The biochemically defined circuits within the ARAS include the adrenergic (epinephrine), noradrenergic, serotonergic, and dopaminergic circuits described in Chapter 15.

The brainstem RF is subdivided at all levels into three zones (*see* **Fig. 22.1**): (1) the lateral zone (lateral one-third of the tegmentum), (2) the medial zone (medial two-thirds of the tegmentum), and (3) the midline zone. The *lateral zone* (also called the "sensory" zone) is composed of small cells with relatively short ascending and descending axons that terminate primarily in the medial reticular zone. The lateral zone is considered to be an afferent and association area because it receives multiple "sensory" inputs from the spinal cord, cranial nerves, and input from the cerebellum and cerebrum. The *medial zone* ("motor" or "efferent" zone) is characterized by the presence of many large neurons whose axons bifurcate into long ascending and long descending branches. These fibers, which emit numerous collateral branches, form the *central tegmental tract* of the brainstem tegmentum. The output from the motor zone is projected rostrally to the hypothalamus and intralaminar nuclei of the thalamus, caudally to the spinal cord via rubrospinal and reticulospinal tracts, posteriorly to the cerebellum, and laterally to cranial nerve nuclei. The *midline zone* comprises primarily the *nuclei of the raphe and the periaqueductal gray* (*see* **Fig. 13.6**). These nuclei, along with the locus ceruleus, have significant roles in the regulation of the levels of consciousness and the stages of sleep (Chap. 21).

Roles and Connections

The RF receives a continuous stream of multimodal "sensory" stimuli. Responsiveness to these inputs is expressed through fluctuations in the expressions of its output. These are revealed in the variety of nuances associated with such behavioral states of the sleep–wake cycle as drowsiness, attentiveness, awareness, and alertness. The monoaminergic neurons of the brainstem, especially those of the raphe nuclei and locus ceruleus, have a significant role in the neural activity that evokes these behavioral expressions (Chap. 15).

Sleep is not just an absence of wakefulness; rather, it is the product of active processes involving the brainstem "ascending reticular activating system" that regulates the level of activation of the brain. Irreversible coma (permanent loss of consciousness) resulting from severe head injury is associated with extensive damage to the cerebral cortex, midbrain reticular formation, or both. A large lesion of the

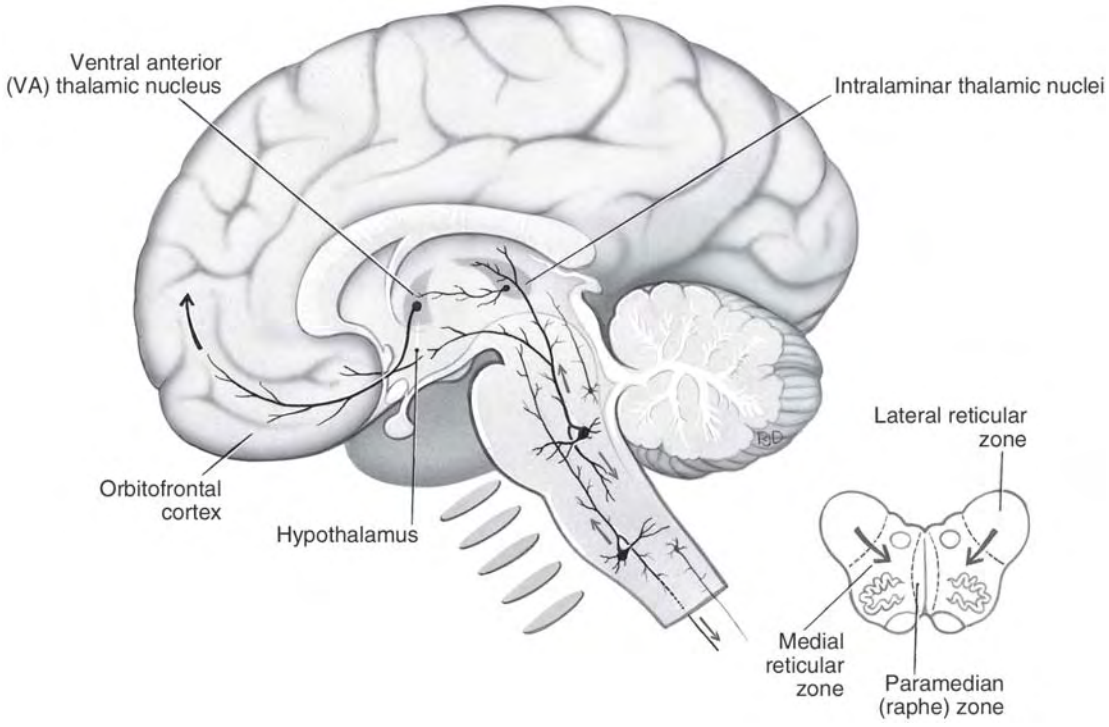


Figure 22.1: The central tegmental tract of the ascending reticular pathway system. In general, the multineuronal, multisynaptic relays of the brainstem reticular formation (located in the tegmentum) extend rostrally into two telencephalic regions: (1) dorsally into the intralaminar, ventral anterior (VA), and dorsomedial thalamic nuclear complexes and (2) ventrally into the hypothalamus. The thalamic component projects to the orbitofrontal cortex via VA. The insets at the lower left represent a series of neuropil "segments." The cross-section through the brainstem (medulla) illustrates the division of the brainstem RF into a midline raphe or paramedian zone, a medial reticular or "efferent" zone, and a lateral reticular or "sensory" zone. Arrows indicate the general direction of flow of neural influences.

midbrain RF produces an animal that is in a constant behavioral stupor or in a coma. In contrast, a lesion in the pontine RF results in an animal that is constantly awake. The brainstem RF exerts powerful influences through specialized nuclear groups for carrying out vital functions. These include cardiovascular centers for control of blood pressure and respiratory centers for regulation of breathing (Chap. 20). The RF contributes to postural control through influences exerted on upper-motoneuron pathways (reticulospinal and vestibulospinal tracts). This is also demonstrated in such tonic and phasic motor actions as expressed in relaxation and fidgeting.

Summation

The RF does look chaotic. Its inputs are heterogeneous and dismayingly convergent. Its output fibers contain few circumscribed bundles and they tend to be widespread and organized diffusely. Yet, many of the effector mechanisms embodied in the reticular formation are highly specific and precise. The heterogeneity of the inputs to the reticular formation can reflect no more and no less than the needs to adapt to cir-

cumstances as diverse as the acidity of blood plasma, the oxygen content of inhaled air, and the amount of physical exertion one undertakes or anticipates undertaking from moment to moment (Nauta and Fiertig, 1986).

LIMBIC SYSTEM

Anatomically, the limbic system comprises a complex network of cortical areas and subcortical structures interconnected by bidirectional pathways. One component of the limbic system, the hippocampus is important in mechanisms of memory. In its role as the emotional processing system (EPS), the limbic system is involved in a variety of functions. (1) *Emotion* as a conscious feeling is mediated largely by processing within the *cingulate and prefrontal cortices*. Emotions are actually bioadaptations that were found to be beneficial during evolution. (2) *Emotional reactions* to aversive stimuli are responses to sudden danger. The initial reflexive reaction is an alerting pose by evoking phylogenetically derived programmed responses that have survival value (e.g., freezing [playing possum]). This generally is a preliminary posture prior to a decision for action—fight or flight. (3) *Emotional reactions* to pleasurable and satiety stimuli are such positive responses as joyful expressions, elements of love in pair bonding, and family organization along with affirmative social interactions. (4) *Emotional actions* are activated by stimuli that evoke the motivational system to drive and to guide goal-directed behavior. These responses are generally mediated by goals (e.g., food, water, and pain). Goal-directed actions range from being motivated by a specific single stimulus to complex abstract ideas or beliefs.

Major limbic centers include the *mesocortex* (cingulate gyrus, orbitofrontal, insular, and medial prefrontal cortices), parahippocampal gyrus, and subcortical structures, including the thalamus, septal area, nucleus accumbens, hippocampus, hypothalamus, brainstem and, of most significance, the *amygdala (amygdaloid complex*).

The mesocortex has a vital role in emotional experiences associated with sensations. The perceptions of fear, anger, pleasure, and satisfactions are considered to be expressions of interactions of the cerebral cortex with subcortical centers focusing on the amygdala and its output. Patients in whom the prefrontal cortex and cingulate gyrus has been ablated illustrate this role in emotional experience. Pain no longer bothers them. Pain continues to be felt as a sensation and activates the expected autonomic responses, but pain is no longer perceived as a decidedly unpleasant experience. Stimulation of the anterior cingulate gyrus results in a variety of responses among which are pain relief, reduction in obsessive–compulsive behavior, impaired initiation of motor activity, apathy, depression, and reduction in anxiety and social awareness.

Substantia Innominata, Basal Nucleus of Meynert, and Extended Amygdala

Rostral to the hypothalamus and globus pallidus and below the anterior commissure is a region of gray matter called the *substantia innominata* within which is the *basal nucleus of Meynert* (*see* **Fig. 22.2**). The substantia innominata has reciprocal connections with the amygdala, hippocampus, and hypothalamus. The basal nucleus has reciprocal linkages with the hippocampus. Projections from large cholinergic neurons of the basal nucleus to the entire neocortex are regarded as significant because they could have a major role in neural processing associated with intellectual functions (Chap. 25). The nucleus could also play a role in modulating the amygdala and the neocortex. The substantia innominata also contains some neurons that, together with cell groups of the bed nucleus of the stria terminalis located in the basomedial forebrain bordering the anterior commissure, are a rostral extension of the central nucleus of the amygdala. The continuum of central nucleus, substantia innominata, and bed nucleus of the stria terminalis is referred to as the *extended amygdala,* which is next to the ventral striatum and ventral pallidum. This emphasizes the close geographic

relationship of limbic structures with parts of the basal ganglia concerned with motor activity related to emotional stimuli (Chap. 24). These could, in part, be reflected by alterations in facial expression displaying fear, happiness, sorrow, anger, and so forth, and in the connotations of posture such as stooped vs erect.

Hippocampal Formation and the "Papez Circuit"

The hippocampal formation consists of the hippocampus proper and the dentate gyrus (*see* **Fig. 22.3**). The subiculum is transitional between the hippocampus and entorhinal cortex (area 28) of the parahippocampal gyrus, and some consider it to be part of the hippocampal formation. The hippocampus forms the floor of the temporal (inferior) horn of the lateral ventricle. The ventricular surface is covered by a thin lamina of axons called the alveus. The fibers of the *alveus* arise from the hippocampus and from the adjacent *subiculum*. These fibers converge to form a flattened band called the *fimbria of the fornix,* which continues as the fornix. The *fornix* with its approximately 1.25 million fibers is the major output channel of the hippocampus; it also contains some fibers traveling in the opposite direction, particularly from the septal region, that terminate in the hippocampus. The hippocampal formation is composed of archicortex (Chap. 25) characterized by the presence of three layers: molecular, pyramidal (granular for the dentate gyrus), and polymorphic (*see* **Fig. 22.3**). The

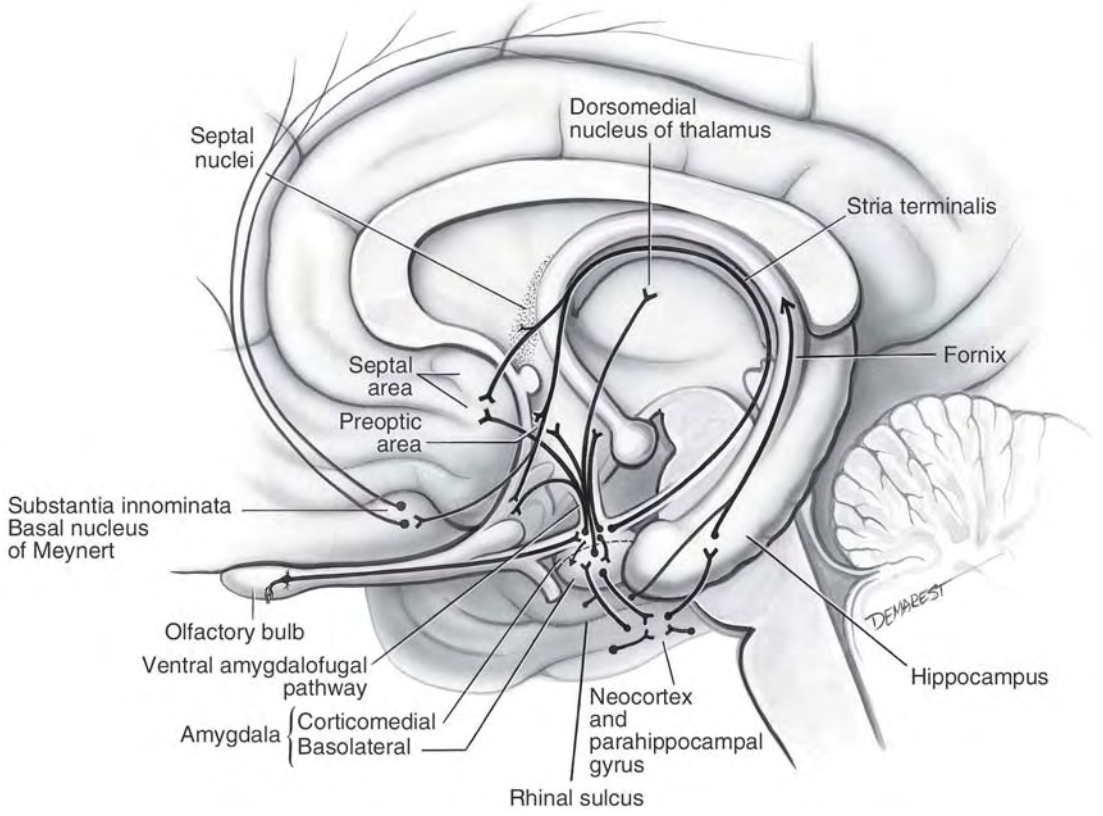


Figure 22.2: Some connections of the limbic system, with emphasis on the circuitry associated with the amygdala. Many of the circuits are reciprocal. Descending fibers terminating in the brainstem reticular formation are not illustrated.

molecular layer is synaptic and mainly consists of a meshwork of axonal, dendritic, and glial processes (neuropil). The *pyramidal layer* of the hippocampus contains several rows of relatively large triangular or pyramidal-shaped cell bodies with axons that enter the alveus and are the main output of the hippocampus. Pyramidal cell apical dendrites extend into the molecular layer along with axon collaterals. Interneurons also are present in the pyramidal layer. For the dentate gyrus, this middle layer is called the *granular layer* because of a dense aggregation of small stellate cells. Dendrites of these cells extend into the molecular layer, and their axons, called mossy fibers, terminate within the hippocampus near the base of pyramidal cell apical dendrites. The *polymorphic layer*, covered by the alveus, is composed mainly of neuropil, like the molecular layer, which includes the extensive basal dendrites as well

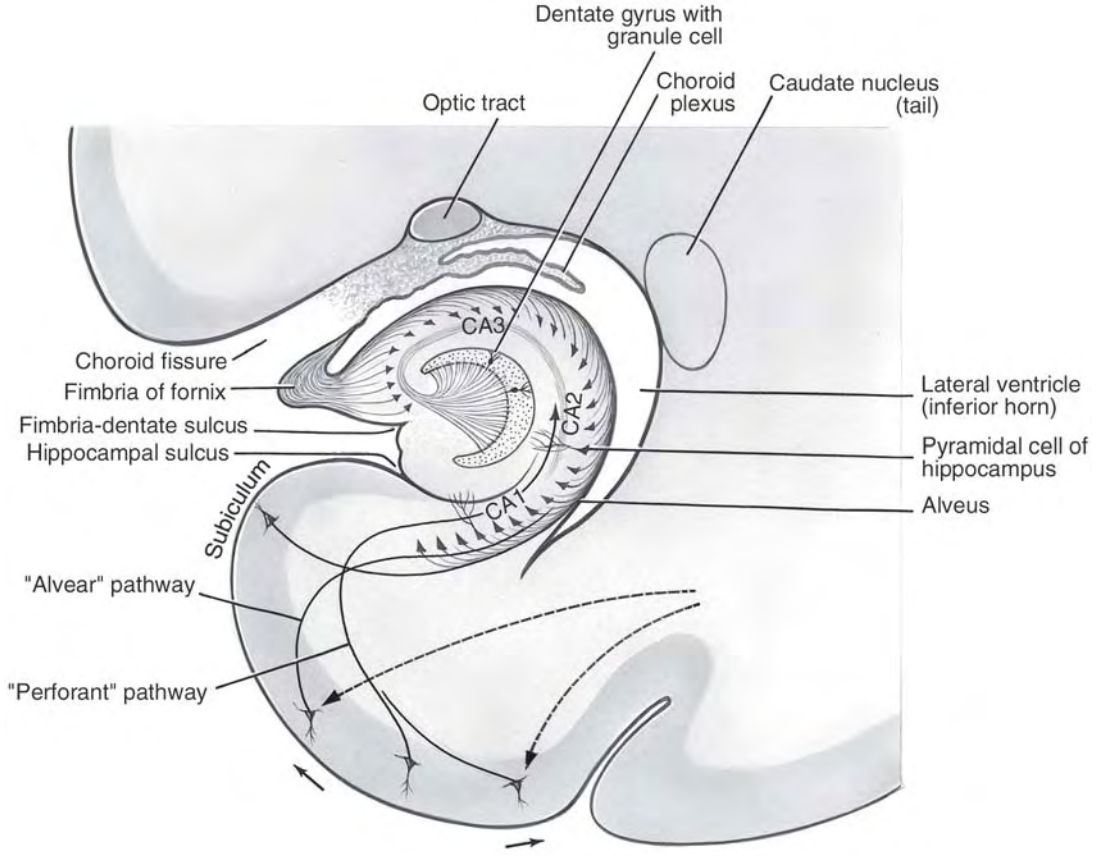


Figure 22.3: Diagram of a transverse section through the hippocampal formation (dentate gyrus and hippocampus), subiculum, and entorhinal cortex (area 28) of the parahippocampal gyrus. (1) Input to the entorhinal area and subiculum is derived from several areas of temporal lobe cortex; (2) output from the entorhinal area projects to the dentate gyrus and hippocampus via the alveus ("alvear path") or via the perforant path; (3) connections of the entorhinal area and subiculum with other cortical areas generally are reciprocal; (4) axons of pyramidal cells of the subiculum and hippocampus pass through the alveus and fimbria into the fornix; and (5) axons of the granule cells in the dentate gyrus terminate in the hippocampus. CA (cornus ammonis) refers to the fields of the hippocampus.

as axon collaterals of Purkinje cells. The hippocampal formation is divided into fields CA1, CA2, and CA3. CA1 is continuous with the subiculum. The designation CA comes from cornu ammonis (Ammon was an Egyptian god with a ram's head), another name for the hippocampus conferred because of its shape in the coronal plane. The hippocampal formation has reciprocal connections with the parahippocampal gyrus, which, in turn, has widespread reciprocal cortical interconnections. Afferents from the medial part of the entorhinal area (area 28) traverse the subiculum and alveus (*alvear pathway*) and terminate on basilar dendrites and cell bodies of pyramidal cells in the subiculum and CA1 (*see* **Fig. 22.3**). Afferents from the lateral part of the entorhinal area pass through the alvear path as the *perforant pathway* and terminate on apical dendrites of pyramidal cells in the hippocampus and granule cells of the dentate gyrus. The hippocampus receives monoaminergic input from the raphe nuclei and the locus ceruleus. The output of the subiculum and hippocampus is conveyed via the fornix to the mammillary bodies, other hypothalamic nuclei, and nuclei in the vicinity of the septal region and the substantia innominata, including the basal nucleus of Meynert. The hippocampus is bilaterally interconnected via fibers that decussate in the fornical (hippocampal) commissure and turn back in the contralateral fornix; some postdecussational fibers continue rostrally in the opposite fornix. The fornix divides around the anterior commissure into precommissural and postcommissural fibers and it is the latter group, arising from the subiculum, that terminates in the mammillary body as well as, to a lesser extent, in the anterior, intralaminar, and lateral dorsal nuclei of the thalamus. The mammillothalamic tract projects from each mammillary body to the anterior thalamic nuclear group; the latter projects to the cingulate gyrus (Chap. 25), as does field CA1 of the hippocampus and the subiculum. Commencing in the cingulate gyrus, multineuronal linkages terminate in the cortex of the parahippocampal gyrus.

The reciprocal connections of the hippocampus with the many areas of the neocortex are critical in its presumed role of receiving novel sensory inputs that are registered as short-term memory. Within a limited-time span, this memory can become a long-term memory. Memory disorders are characteristic features of lesions of the hippocampus. Electrical stimulation of the hippocampus elicits fear, memories, illusions, and emotions, but this might, in part, be the result of the activation of other structures.

The classic *Papez circuit* for emotions (1937) comprises the sequence of hippocampus → fornix → mammillary body → mammillothalamic tract → anterior thalamic nuclear group → cingulate gyrus → parahippocampal gyrus and neural linkages back to the hippocampus (*see* **Fig. 22.4**). It was recognition of the closed nature of this loop that led Papez to refute the long-held notion that the hippocampus served in some obscure way the olfactory sector of functions. Input to the parahippocampal gyrus and hippocampus is derived from the cingulate cortex and from association areas of the cerebral cortex (Chap. 25). Papez regarded the cingulate cortex "as the receptive region for the experiencing of emotion." However, the hippocampus in particular is important for induction of short-term memory. Long-term potentiation, which facilitates synaptic plasticity, a prerequisite for memory, is associated with the hippocampus.

Functional Subdivisions of the Limbic System

In 1952, Paul MacLean proposed the term *limbic system* (LS) when he reintroduced Papez' concept that certain limbic structures could be neuroanatomic substrates for emotion. On the basis of experimental data, he established a major foundation for our current understanding of the limbic system. In brief, MacLean proposed that (1) cortical and hypothalamic information is integrated in the LS; (2) the limbic system is the target of multisensory inputs; (3) he downplayed the previously held view that olfaction and the so-called smell brain played a dominant role in the functioning of the LS to a significant but sub-

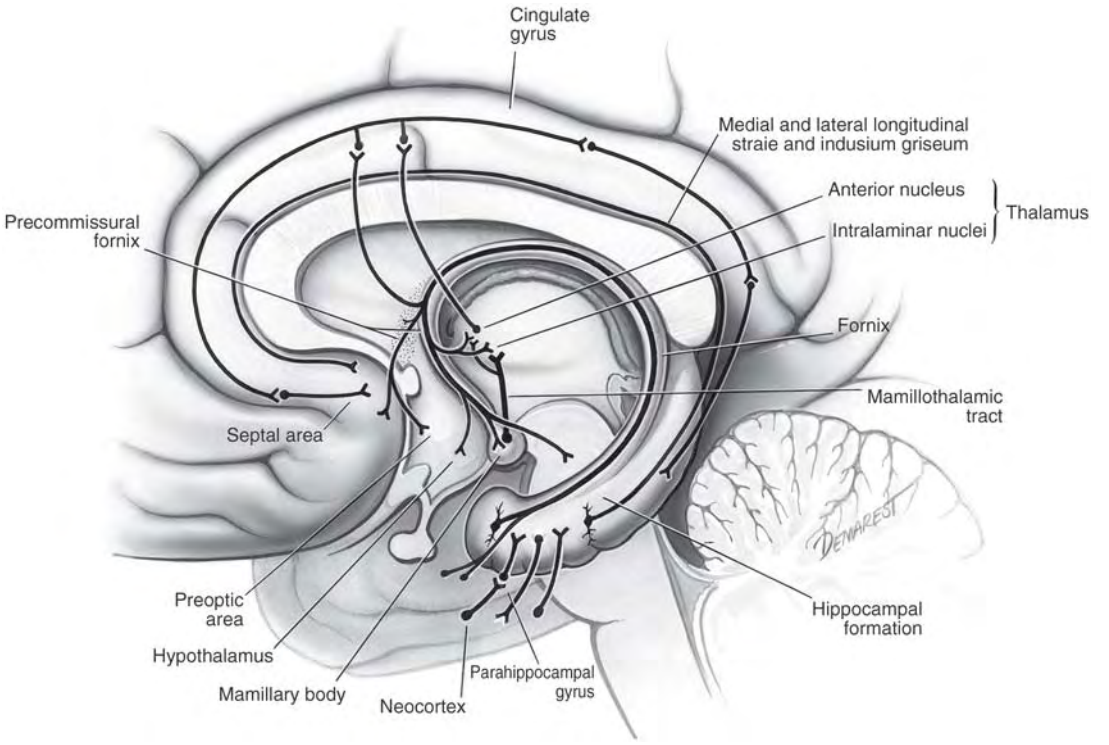


Figure 22.4: The "Papez circuit" includes the hippocampus via fornix → mammillary body via mammillothalamic tract → anterior thalamic nuclear group → cingulate gyrus → parahippocampal gyrus → hippocampus. The subiculum is a pivotal cortical area projecting to widespread regions of the cerebrum. Many connections are reciprocal.

ordinate position; (4) the amygdala, nucleus accumbens, septal area, and orbitofrontal cortex are vital in the regulation of emotion. MacLean's influential theory asserted that the cingulate cortex, along with the neocortex, can be identified with forms of emotional behavior that illustrate the evolutionary transition from the primitive brain of therapsid (mammal-like) reptiles to the early mammalian brain during the geologic Paleozoic Era and then to the highly evolved neocortex of mammals, including humans during the Cenozoic Era. According to this theory, the evolution of the LS enabled mammals to experience and expresses emotions and, thus, emancipated them from stereotypic behaviors dictated by the brainstem (often referred to as the reptilian brain). In this schema, the evolution of the neocortex gives higher mammals and especially humans the capacity for problem solving and rational thought.

The Septal and Amygdala Pathways

MacLean (1955) delimited two functional subdivisions within the LS: (1) The septal pathway includes the septal area, anterior cingulate cortex, stria terminalis, hippocampus, and *amygdala***,** which are associated with memory related to social and sexual behaviors, including mating, procreation, and care of offspring. These are important for the preservation of the species. Stimulation of the septal area results in pleasurable feelings, euphoria, and sexual arousal leading to an orgasm. (2) The amygdaloid pathways, including amygdala and neocortex, have a presumptive role in behaviors

such as fighting, feeling, feeding, and other appropriate visceral functions that contribute to *self-preservation*.

The Mesolimbic and Mesocorticolimbic Systems

1. The mesolimbic dopaminergic pathway originating in the ventral tegmental area (VTA) of the midbrain (*see* **Fig. 13.15**) and projecting to the nucleus accumbens, or *ventral striatum* (Chap. 24), is of paramount importance because of the extensive connections of the latter to subcortical nuclei of the LS. Acting at the *limbic–motor interface,* the nucleus accumbens projects emotion information via the *stria terminalis* to the *dorsal striatum,* where emotions are translated into ongoing motion actions of the motor-oriented striatum (e.g., at times expressed as short phasic bursts of activity).
2. The mesocortical dopaminergic system pathway, which projects directly from VTA to mesocortex, is involved in emotions, memory, and positive reinforcement of emotional behaviors. In turn, the mesocortex has connections with the *amygdala*, which, via reciprocal connections, links the cortical areas (mesocortex) involved with conscious feelings (e.g., fear) with the hypothalamus (Chap. 21) and brainstem circuitry involved with somatic and visceral emotional motor-associated expressions (e.g., facial, vocal, and changes in blood pressure).

The Rostral and Caudal Limbic Systems of MacLean

1. The *rostral limbic system*, which is thought to be functionally involved with emotional expressions, is anatomically comprised of the amygdala, septal nuclei, orbitofrontal and medial prefrontal cortex, anterior insula, and anterior cingulate gyrus.
2. The *caudal limbic system,* which is presumed to be associated with memory and some visual functions, consists of the hippocampus, parahippocampal and posterior cingulate gyri, septal area, and the dorsomedial thalamic nucleus.

Overview of Functional Neuroanatomical Organization of the Limbic Circuitry and the Role of the Amygdala

The LS is a scattered complex neuroanatomical network of largely bidirectional pathways linking cortical areas and subcortical structures (*see* **Figs. 22.2 and 22.5**) with roles (1) in the perception of emotional feeling and motivation and (2) in the regulation of the expression of emotional behaviors (e.g., aggression, fear, and sexual behaviors). The anatomical structures involved in the limbic circuitry include the cerebral cortex, along with the subcortical septal area, hippocampus, nucleus accumbens, dorsomedial thalamic nucleus, striatum, and ventral tegmental area of the midbrain, The multifaceted processing of "limbic" information within the limbic circuitry converges and coalesces for additional processing within the amygdala. Thus, the *amygdala* emerges as the defining hub and nodal center that couples the neocortical and mesocortical areas highly processed sensory information with the subcortical nuclei of the limbic circuitry. In turn, the amygdala sends its output to the thalamus, hypothalamus, and brainstem, where endocrine and autonomic responses associated with emotional expressions are evoked.

The amygdala utilizes a vast array of sensory information in the performance of its functional roles. The neocortex provides the amygdala with complex highly processed sensory information derived from the visual, auditory, somatosensory, and visceral systems. Less processed sensory information received by sensory relay nuclei of the thalamus (e.g., medial geniculate nucleus) from ascending spinal and brainstem sensory pathways (e.g., lateral lemniscus) is sent directly to the amygdala. This low-level information is utilized in immediate "essentially reflex" responses to aversive stimuli (LeDoux, 2002). Information derived from the mesocortex and the hippocampus is processed within the amygdala for roles in emotion, learning and memory formation associated with the perceptions of emotion and feelings. The amyg-

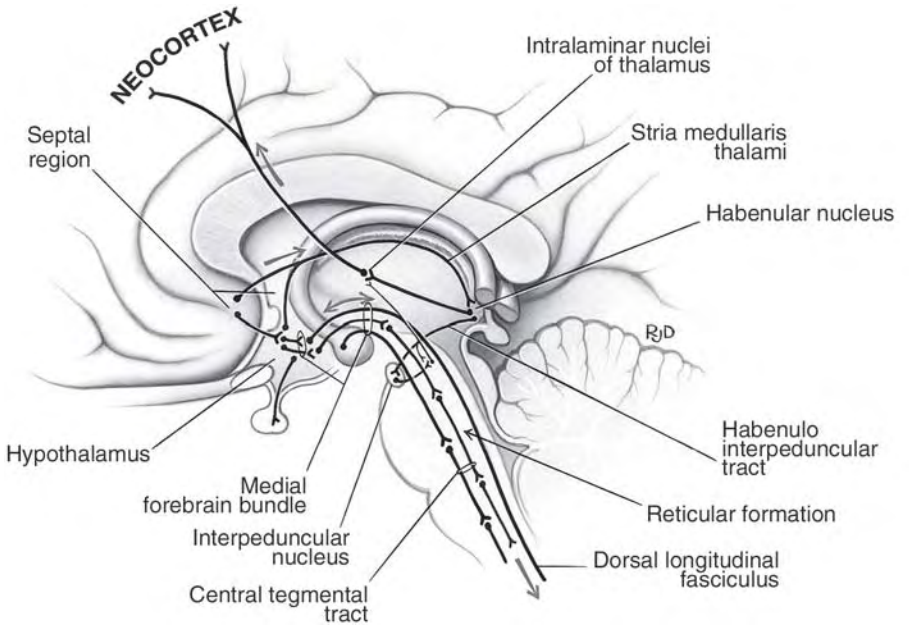


Figure 22.5: Some connections of the LS. The medial forebrain bundle is a multineuronal pathway extending from the septal area through the lateral hypothalamus to the brainstem tegmentum. Note the pathway system comprising the sequence of septal area and preoptic area → habenular nucleus → midbrain tegmentum and interpeduncular nucleus. The latter projects to the midbrain tegmentum.

dala receives inputs from the olfactory bulb both directly and indirectly via the piriform (olfactory) cortex (Chap. 13). Odors are significant energizers of the LS.

The amygdala projects output for the expression of emotion (1) via the stria terminalis to the *hypothalamus–pituitary* complex for the regulation of stress hormone release, to the *lateral hypothalamus* for sympathetic regulation, and to the *striatum* to modulate the motor expressions of emotion and (2) via ventral amygdalofugal projections to the nucleus of the solitary tract, pontine parabrachial nucleus, and reticular function involved in autonomic regulation (Chaps. 15 and 20). Thus, the amygdala, through its output, regulates hypothalamic and brainstem effector systems and their roles in the expression of emotional behaviors involving endocrine hormone release and the somatomotor and autonomic nervous systems.

The cingulate gyrus and the orbitofrontal and medial prefrontal cortex in part mediate the conscious perception of emotion (feelings). These cortical areas have reciprocal connections with the amygdala, which is the neuronal center that is the hub of the subcortical limbic circuitry. The amygdala through its output is responsible for generating emotional states and mediating peripheral autonomic, endocrine, and skeletomotor responses. The amygdala has reciprocal connections with autonomic nervous system regulatory centers of the brainstem, including the periaqueductal gray, parabrachial nucleus, vagal nuclei, and the reticular formation. The conscious experience of emotion includes fear, anger, fright, pleasure, or contentment. The emotional state is evident in a variety of responses: increase in blood pressure, dilation of the pupil, inhibition of gastrointestinal contractions, dryness of the mouth, sweaty palms, stress effects from stress

hormones such as cortisol and somatic motor responses such as nervous tics.

The Processing Triangle of Basolateral Nucleus of the Amygdala, Nucleus Accumbens, Dorsomedial Thalamic Nucleus

Within the limbic system, there are many complex circuits providing communication between centers. Limbic structures, modulated by dopamine, are referred to as mesolimbic because the origin of dopamine is the mesodiencephalic ventral tegmental area, located in contiguity with the substantia nigra. It is within limbic circuitry where emotional and internal states are coordinated and coupled—the driving forces behind changes in motivational state. The mesolimbic network is involved in recognizing incentives that reinforce behavioral response patterns. The following is a schematic representation of interactions within a presumed triangular circuit, which includes the basolateral nucleus of amygdala, mesocortex, nucleus accumbens, and the dorsomedial nucleus of the thalamus. The amygdala emits fibers to the neocortex and dorsomedial thalamus which project to the mesocortex forming a loop. The mesocortex, thalamus, and amygdala each send input to the nucleus accumbens. Striatopallidal projections go to the dorsomedial thalamus/prefrontal cortical circuit and to VTA, the major source of dopamine innervation of the mesolimbic system. In healthy individuals, the mesolimbic striatal networks reinforce drives behind motivation to behaviorally adapt to demands imposed on the organism.

Positron-emitting tomographic (PET) scan imaging of a human with *clinical unipolar depression* revealed abnormal blood flow within the three sides of the triangle: the amygdala, orbitofrontal and medial prefrontal cortex, and the DM. The blood flow returned to normal following the patient's subjective recovery from the depression (Brevets and Raichle, 1999).

Clinically depressed patients formulate thoughts of gloom and doom. They ideate suicide stemming from feelings of sustained sadness. Fatigue, lethargy, listlessness, and unremitting emotional distress relate pathophysiologically to high rates of visceral and immune disorders. Pathology of the mesolimbic network reflects deeply rooted suppression of the basic drives to cope with ongoing environmental demands. Severely depressed and suicidal patiens are goal-driven to escape the agony of despondency. A behaviorally sensitized hyperdriven defense arousal network causes overproduction of hypothalamic/pituitary/adrenal stress axis hormones such as cortotropic releasing hormone, resulting in increased sympathetic output to the heart, gut, and immune organs. Damasio (2003) defined an emotion as a set of changes in body and brain states that occur in many organs, and in some brain circuits, under the control of a dedicated brain system, which responds to the content of one's thoughts relative to a particular entity or event. A story may literally be constructed to explain "adaptive and mal-adaptive" action tendencies, variably influencing our moods and affect. Learning from experiences may permanently alter perceptions and propensities to think, proact, and act in specific ways.

Amygdala: The Nodal Processing Center of the Subcortical Limbic Circuitry (*see* Fig. 22.2)

The almond-shaped *amygdala (amygdaloid complex*) is located within the tip of the temporal lobe deep to the uncus and rostral to the hippocampus. The amygdala is the key structure involved in analyzing and processing the emotional and motivational significance of an array of sensory stimuli and, in turn, coordinating and activating several neuronal systems that mediate inborn and acquired responses with an emotional nuance. The amygdala receives inputs from several sources: (1) Stimuli signaling immediate dangers that are directly and rapidly conveyed as low-level processed information from the thalamus to the amygdala to evoke primitive rapid responses. As the centerpiece of the limbic defense system, the amygdala determines and evaluates whether danger, innate or learned, is present and then initiates bodily responses that were designed during

evolution to deal with the danger. (2) Signals conveying highly processed information from major sensory areas of the cortex are indirectly conveyed to the amygdala to produce more measured and modulated emotional responses, as demonstrated by acquired classical conditioning. (3) Stimuli signal information from the hippocampus, basal ganglia and other subcortical centers to the amygdala that contribute to the quality of the responses. The amygdala exerts its motor influences via circuitry to effector centers of the hypothalamus and brainstem (*see* **Fig. 22.5**). In general, the amygdala modulates the somatic and visceral components of the peripheral nervous system and fine-tunes the organism's responses to ongoing stimulation.

The amygdala is essential for sensing and evaluating the affective significance of incoming stimuli and activating the appropriate responses for its three principal functional roles: (1) behavior for preservation of self, (2) learning, and (3) emotion processing. Self-preservation behavior is a universal motive in which aversive stimuli are processed by the amygdala and projected to produce fight or fright activity, including endocrine hormone release and somatomotor and autonomic emotional responses. As for learning, the amygdala is in a central position to associate and to coordinate a variety of diverse sensory inputs that generate new behavioral and autonomic responses. This is demonstrated in learning classical conditioned emotional responses. Emotion processing is a subtle activity. PET scan studies show increased activation of the amygdala while viewing a motion picture showing an airplane crash. Intracranial recording studies of monkeys indicate that amygdaloid activity is enhanced with the increasing emotional significance of stressful stimuli. Amygdalectomized monkeys become socially isolated from their troop and are transformed into depressed loners.

The Amygdala Contains Three Major Nuclear Groups. The role of the amygdala is to mediate neural processes that encompass somatic and visceral sensory experience with emotional significance. The amygdala consists of three major groups: (1) a corticomedial nuclear group, (2) a basolateral nuclear group, and (3) a central nuclear group. The groups have reciprocal connections with the neocortex, thalamus, hippocampus, hypothalamus, and brainstem.

The *corticomedial nuclear group* (CMG) receives major input from the olfactory bulb and piriform cortex (Chap. 14) and, in addition, from other limbic centers via the stria terminalis. The CMG projects via the stria terminalis to limbic centers such as the septal area and the hypothalamus. The olfactory input does not involve the perception of smell, but, rather, the subtle to intense emotional and motivational associations evoked by odoriferous stimuli (e.g., odor-related responses to the smells of food and perfume). The olfactory system is more than just a perceiver of odors; it can be an activator and a sensitizer involved with triggering behavioral patterns. The perception and discrimination of smell is associated with the uncus (*see* **Fig. 1.7**). A lesion in the region of the uncus could cause epileptic seizures known as "uncinate fits" that are preceded by an olfactory aura. The amygdala might have a role in appetite and appetitive behavior through its projection to the ventromedial nucleus of the hypothalamus (Chap. 21).

The enlarged *basolateral nuclear group* (BLNG) in humans receives significant input pertaining to all of the sensory modalities from the thalamus and the cortex. Following processing within the BLNG, information is sent to the central nuclear group (CNG), which is the main source of output from the amygdala. The BLNG also receives low-level processed sensory information directly from all sensory nuclei of the thalamus (e.g., medial geniculate nucleus and ventral posterior nucleus; Chap. 23). The BLNG receives significant higher-level processed complex information of all modalities involved with the visual, auditory, and tactile senses from the primary sensory and association cortical areas. The BLNG also is reciprocally con-

nected with the anterior cingulate gyrus and orbitofrontal cortex, important in integration of emotions such as fear and anxiety into the various emotional expressions. Thus, the amygdala mediates processes that invest sensory experiences with emotional significance. In addition, the amygdala influences conscious emotion and feeling via its projections to the cingulate gyrus and prefrontal cortex. The BLNG sends processed information to the CNG. The latter gives rise to fibers that project out of the amygdala via the stria terminalis and ventral amygdalofugal pathways.

The CNG is reciprocally connected with the mesocortex, nucleus accumbens, hypothalamus, and brainstem, including visceral sensory relay nuclei such as the solitary, parabrachial, and dorsolateral tegmental nuclei and the locus ceruleus, in addition to being the major recipient of the processed output from the basolateral nucleus. The CNG is thought to be involved in mechanisms associated with both the acquisition and display of fear and anxiety. It has a significant role in arousal and the conscious perception of emotion. The latter is related to its interconnections with the anterior cingulate gyrus and orbitofrontal cortex. Linkages of the CNG with the basal nucleus of Meynert in the basal forebrain and with the hippocampus might contribute to the suggested roles of these two centers in attention and memory. The central nucleus of the amygdala has two output channels: (1) the stria terminalis and (2) the ventral amygdalofugal pathways (*see* **Fig. 22.2**). The projection to the mesocortex enables the central nucleus to exert an important role in arousal and the conscious perception of emotion. The output via the stria terminalis to the paraventricular nucleus of the hypothalamus might be significant in mediating neuroendocrine responses during fearful and stressful stimulation.

Experimental evidence indicates that, collectively, all of the nuclear groups of the amygdaloid complex are critical processing centers involved with arousal, conscious perception of emotion and emotional expressions, olfaction, and control of visceral functions. Electric stimulation of the amygdala in the living subject can result in bradycardia, alteration in respiration, pupillary dilatation, and urination, influences mediated via the hypothalamus.

The Mesocorticolimbic System, Mesolimbic System, and Nucleus Accumbens

The mesocorticolimbic system (MCLS) and mesolimbic system (MLS) are dopaminergic systems that gate signals involved in the regulation of motivation and biological drives. Motivation is the spontaneous drive or incentive that refers to the neuronal and physiological factors that initiate, sustain, and direct behavioral responses. The basic and homeostatic expressions of motivation are directed by such *biological drive states* as hunger, thirst, and temperature. Drive states are characterized by tension and distortions relevant to a physiologic need, followed by the *reward of* relief when the need is consummated.

The MCLS and MLS projections to the nucleus accumbens, striatum, and cerebral cortex are conceived as modulatory systems concerned with the process of motivation. The MLS is associated with the biological drives expressed as responses for reward (as positive or incentive reinforcement) or to fear (as negative or aversive reinforcement). The MCLS is involved with normal cognitive functions (e.g., attention) and social behavioral responses.

Dopamine is the transmitter identified with the MCLS and MLS pathways and has long been considered to be the critical factor in motivation and reward. The release of dopamine is (1) important in the initiation and maintenance of anticipatory behaviors in the presence of incentive stimuli, (2) involved in notifying limbic cortex that something novel or unexpected has occurred, and (3) involved with the switching of attention and selection of action. The relatively few dopaminergic neurons in the human brain are all located in the midbrain. They are equally divided between (1) the substantia nigra that gives rise to the nigrostriatal pathway (Chap. 24) and (2) the ventral tegmental area, which activates the MCLS and MLS projections to the nucleus accumbens, amygdala, striatum,

hippocampus, anterior cingulate gyrus, and mesocortex. In addition to dopaminergic input from the ventral tegmental area (VTA), the amygdala, nucleus acccumbens and other centers receive *noradrenergic inputs* via the medial forebrain bundle from the locus ceruleus and *serotonergic inputs* from the dorsal raphe nuclei of the brainstem (*see* **Fig. 22.5**).

Functionally, these systems comprise the neural network for interactions between the cerebral cortex information processing and the effectors in the hypothalamus and brainstem autonomic centers that modulate endocrine-release and motor-system-regulating behaviors. The centers are organized as a unified system linked together by reciprocal projections.

Mesocorticolimbic System. The dopaminergic mesocorticolimbic system originates in the VTA and projects to the cortex, particularly to prefrontal and the anterior cingulate gyrus. This system is involved in the positive reinforcement of such activities as feeding, drinking, sexual activity, and drug abuse (cocaine, opiates, alcohol, and marijuana). The prefrontal cortex is involved in the organization of activities associated with rewards, motivation, planning, attention, and social behaviors (Chap. 20). In addition, rostral projections from the amygdala to the anterior cingulate gyrus and the orbitofrontal cortex contribute to arousal and the conscious perception of emotion. Arousal is also enhanced by interconnections with the adrenergic locus ceruleus and the VTA, as well as by connections with the basal nucleus of Meynert. In humans, dysregulation of the MCLS is associated with the positive and negative symptoms of schizophrenia that bear some resemblance to the defects seen after surgical disconnections of the prefrontal lobes. After the loss, subjects are poorly motivated and exhibit a flattened affect.

Mesolimbic System. The *mesolimbic system* projects from the VTA largely to the nucleus accumbens, amygdala, and, in addition, the bed nucleus of the stria terminalis, lateral hypothalamus, hippocampus, and septal area. The nucleus accumbens receives important input from the hippocampus, frontal lobe, VTA, amygdala and some thalamic nuclei. Following processing, the nucleus accumbens projects output to the autonomic regulatory centers, the globus pallidus, pedunculopontine nucleus, and hypothalamic nuclei involved in emotional expression.

The nucleus accumbens is located at the crossroads of emotions and movement, where the limbic emotions are translated into the movement actions influenced by the striatum. The nucleus accumbens is the recipient of a considerable amount of dopaminergic input from the VTA along with inputs from limbic centers involved in emotion processing such as the amygdala. Acting at this regional interface where emotions are translated into actions, dopamine facilitates synaptic transmission in the output pathways from the nucleus accumbens to the ventral pallidum (Chap. 24). This modulates the movement control regions of the cortical motor cortex and of the brainstem autonomic control centers. These connections are thought to exert a role in planning and integrating movement and emotional stimuli. In summary, the nucleus accumbens and its connections with other nuclei regulate motivation, biological drives, and reinforcement (strengthening) of goal-directed behaviors.

Schizophrenia and the Limbic System

Schizophrenia is a mental disorder that features a disturbance of cognitive and sensory processes leading to hallucinatory experiences, delusions, and disturbances of thought. In addition, the illness shares many features such as paranoia, suspiciousness, and unrealistic thinking. This serious disorder is characterized by a loss of contact with reality (psychosis).

Patients with lesions of the prefrontal cortex have behaviors indicative of a diminished ability to plan and to organize daily activities. In contrast, their general intelligence, perception, and long-term memory is essentially intact. The prefrontal lobe of humans and primates have a predominantly mesocorticolimbic dopaminergic innervation. The depletion of dopa-

mine from this cortex has effects similar to that of lesions. Disturbances of the dopaminergic systems are presumed to contribute to the symptoms of schizophrenia.

Current thinking concerning the etiology of schizophrenia involves a genetic component and combinations of prenatal and postnatal insults to the developing brain. A series of damages occurring in the developing dopaminergic system is thought to contribute to the clinical symptoms of hallucination and delusions by the release of excessive amounts of dopamine.

One theory accounting for the symptoms of schizophrenia involves the interactions of disturbed dopaminergic pathways of the mesocorticolimbic system with the mesolimbic systems (Weinberger et al., 1992). This concept suggests (1) an increase in the activity of mesolimbic projections involving certain dopamine receptor subtypes can account for positive symptoms (e.g., hearing voices), (2) a decrease in the activity of the *mesocortical* connections through the dopamine receptor subtypes in the prefrontal cortex can account for the negative symptoms (e.g., flattening of emotions), (3) an imbalance between mesolimbic and mesocorticolimbic dopamine transmission underlies the development of the schizophrenia through development time, and (4) the activity of the mesocortical pathway to the prefrontal cortex normally inhibits the mesolimbic pathway by feedback inhibition and that the primary defect in schizophrenia is a reduction in this activity, which leads to disinhibition and overactivity in the mesolimbic pathway.

ROLE OF THE LIMBIC SYSTEM

The limbic system is involved with many of the expressions that make us human, namely emotions, behavior, and states of feeling. However, the limbic system is not independent: it interacts with sensory pathways and primary and association cortical areas regarded as playing a primary role in cognitive processes. Different feelings and emotions appear to involve more than one pathway; for some the right hemisphere is thought to be more important.

Stimulation of Structures Within the Limbic System

Electric stimulation of the amygdala and nearby regions in the unanesthetized monkey produces a number of responses. Activities associated with feeding and nutrition are elicited, including sniffing, licking, biting, swallowing, and retching movements. Monkeys exhibit *agonistic behavior patterns*, which comprise behaviors manifested by animals in an attack-and-defense contest during fight or fright. The peaceful monkey becomes a furious and aggressive animal that attacks and bullies; once the stimulus is turned off, the peaceful monkey reappears. Similar observations have been made in humans. In monkeys, increased secretion of digestive juices in the alimentary canal after repeated acute stimulations of the amygdala might be followed by the appearance of gastric erosions similar to peptic ulcers. The possibility of psychic factors in the production of peptic ulcers in humans is implied. Although the role of the amygdala in aggressive behavior is striking, its role in the acquisition and expression of fear or emotional memories is meaningful.

Stimulation of the hippocampal formation produces respiratory and cardiovascular changes, along with a generalized arousal response. In addition, the hippocampal formation acting as a supplemental motor area activates somatic movements such as facial grimaces, shoulder shrugging, and hand movements, characteristic of normal behavioral gestures.

Responses indicative of autonomic activity are evoked by stimulation of the cingulate gyrus and septal area. These responses, observed in humans, include changes in the tone of the blood vascular system, in respiratory rhythms, and in the activity of the digestive system.

Aggressiveness can be inhibited or decreased in monkeys by stimulating the septal area. Stimulation of a “boss” monkey with implanted electrodes reduces its aggressive behavior. If stimulation is prolonged over a

period of days, the other monkeys of the colony sense this change. They lose their fear of the "boss" and take new liberties, such as invading its territory and securing a larger share of food. The former situation returns after stimulations cease. Experimental studies of groups of monkeys reveal that the male boss monkey experiences more stress because of the compulsion to maintain his dominant status than are the less dominant members of the group.

Reinforcement and Reward: "Pleasure Centers" and "Punishing Centers"

Reinforcement refers to the ability of certain events (e.g., stimuli) to strengthen and modify the preceding stimulus–response event. The neural circuitry involved in intracranial self-stimulation (ICSS) with implanted electrodes underlies the natural biological reinforcements and rewards associated with eating, drinking, sex, and drug addiction. The stimulation of large number of limbic sites can elicit, by direct electrical stimulation, rewarding effects and responses. Among these are the medial forebrain bundle, a most responsive pathway, and the septal area, VTA, nucleus accumbens, portions of the amygdala, anterior cingulate gyrus, hippocampus, and dorsal pons. *The featured player in the limbic circuitry* of *the MCLS and MLS is dopamine,* which *has been* implicated in the motivational processes of reinforcement and reward. In addition, there is evidence supporting the concept that dopamine is significant not only in mediating ongoing pleasurable aspects of a reward but also mediates the arousal effects that anticipates an impending reward. Dopamine release increases in the nucleus accumbens in the presence of food, drugs of abuse, and sexual behaviors. Lesions of the nucleus accumbens or drugs that block dopamine receptors decrease or block reinforced behavior activity.

Stimulation by implanted electrodes of certain limbic regions drives an animal to seek further stimulation by tripping a lever over and over again, an expression of positive reinforcement. Such nodal sites have been named "pleasure centers" or "reward centers." Stimulation of other sites causes the animal to avoid further stimulation, an expression of negative reinforcement. Such sites have been named "punishing centers" or "aversion centers." The so-called pleasure centers are in the septal area, subcallosal area, cingulate cortex, hippocampal formation, amygdala, hypothalamus, midbrain tegmentum, and anterior nuclei of the thalamus. Punishing centers are in the midbrain tegmentum and in certain loci in the thalamus and hypothalamus.

Several human subjects whose septal areas were stimulated experienced feelings of pleasure or a "brightening of their attitude." They giggled, talked more, and expressed themselves more freely when the current was on. In humans, psychomotor seizures, which originate in or propagate through limbic pathway connections, are characterized by an aura of fear and visceral sensations, loss of consciousness, and performance of automatic motor acts such a chewing and picking at clothes or nervous pacing about. The subject might even drive a car or carry on a limited conversation, but will not remember any of these episodes. The complex behavioral patterns resulting from limbic stimulation contrast with the relatively simple contralateral muscle contractions or twitches elicited by stimulation of the precentral motor cortex.

Klüver–Bucy Syndrome

Monkeys with the anterior tip of the temporal lobes ablated bilaterally exhibit a constellation of activities and expressions associated with emotion known as the *Klüver–Bucy syndrome*. With bilateral loss of the amygdala, uncus, anterior temporal cortex and portions of the hippocampal formation, the animal is apparently released ("*release phenomenon*") from expressing fear. Wild and aggressive monkeys become tame and docile. The marked absence of emotional responses, such as anger, is accompanied by a loss of facial expressions and vocal protests usually noted during aggressive activities. Monkeys are normally afraid of snakes, but, with this

syndrome, they will now pick up, handle, and examine a live snake with ease. The animal is able to see and to locate objects visually, but is apparently unable to fully recognize the objects by sight. This visual agnosia in humans with a comparable ablation is characterized by the loss of ability to recognize friends and familiar places (Chap. 25). Animals in this state probably have auditory and tactile agnosias. Such animals exhibit strong *oral tendencies*, expressed as a compulsion to examine objects repeatedly with their lips and mouth. These overreacting animals are said to be *stimulus bound* with an irresistible impulse to touch, smell, and taste the object many times. An explanation for this behavior is that because of the agnosia, the animal keeps trying to obtain additional clues in a concerted attempt to identify the familiar object that it cannot recall. Evidence suggests that the stimulus-bound behavior occurs with the removal of the amygdala only. Hypersexual behavior is marked, with many manifestations of autosexual, homosexual, and heterosexual activities.

Korsakoff's Syndrome and Ablations of the Hippocampus

Patients with a form of amnesia, known as *Korsakoff's syndrome*, have pathology in neural complexes associated with the limbic system, namely the mammillary bodies of the hypothalamus and the dorsomedial nucleus of the thalamus. This affliction is the consequence of chronic alcoholism and thiamine deficiency. The patient displays profound memory loss and becomes easily confused. People who have undergone bilateral removal of the anterior temporal lobe, including the amygdala and the hippocampus, also exhibit the symptoms. The patient forgets to answer a question just asked or might reply with an irrelevant answer (called *compensatory confabulation*). Patients with this psychosis learn slowly, but once the subject matter is mastered, they appear to forget at a normal rate. One concept suggests that the memory deficits are the result, in some degree, of defective neural processing (encoding) at the time of learning rather than exclusively to a flaw in memory retrieval. Patients with bilateral lesions involving the uncus and amygdala, and sparing the hippocampus, do not have memory disturbances. Conversely, a bilateral lesion restricted merely to a portion of the hippocampus suffices to impair memory without affecting other aspects of cognitive activity.

SUGGESTED READINGS

Bechara A, Damasio H, Damasio AR. Role of the amygdala in decision-making. *Ann. NY Acad. Sci.* 2003;985:356–369.

Braak H, Braak E, Yilmazer D, Bohl J. Functional anatomy of human hippocampal formation and related structures. *J. Child Neurol.* 1996;11: 265–275.

Brady AM, O'Donnell P. Dopaminergic modulation of prefrontal cortical input to nucleus accumbens neurons in vivo. *J. Neurosci.* 2004; 24:1040–1049.

Brodal A. *The Reticular Formation of the Brain Stem; Anatomical Aspects and Functional Correlations.* Edinburgh: Oliver and Boyd; 1957.

Charney DS, Nestler EJ, Bunney BS, eds. *Neurobiology of Mental Illness.* New York: Oxford University Press; 2nd ed.; 2003.

Damasio A. Feelings of emotion and the self. *Ann. NY Acad. Sci.* 2003;1001:253–261.

Damasio A. *Looking for Spinoza: Joy, Sorrow, and the Feeling Brain.* Orlando, FL: Harcourt; 2003.

Darwin C, Ekman P, Prodger P. *The Expression of the Emotions in Man and Animals.* London: HarperCollins; 3rd ed.; 1999.

Davis M. The role of the amygdala in fear and anxiety. *Annu. Rev. Neurosci.* 1992;15:353–375.

de Olmos JS, Heimer L. The concepts of the ventral striatopallidal system and extended amygdala. *Ann. NY Acad. Sci.* 1999;877:1–32.

Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. *Brain* 1995:118(Pt. 1):279–306.

Gloor P. *The Temporal Lobe and Limbic System.* New York: Oxford University Press; 1997.

Grace AA. Gating of information flow within the limbic system and the pathophysiology of schiz-

ophrenia. *Brain Res. Brain Res. Rev.* 2000; 31:330–341.

Insel TR, Young LJ. The neurobiology of attachment. *Nat. Rev. Neurosci.* 2001;2:129–136.

Kluver H, Bucy PC. Preliminary analysis of functions of the temporal lobes in monkeys. *J. Neuropsychiatry Clin. Neurosci.* 1997;9:606–620 (reprint of 1939 article).

LeDoux JE. Emotion circuits in the brain. *Annu. Rev. Neurosci.* 2000;23:155–184.

LeDoux JE. *Synaptic Self: How Our Brains Become Who We Are.* New York: Viking; 2002.

MacLean PD. The limbic system ("visceral brain") and emotional behavior. *AMA Arch. Neurol. Psychiatry* 1955;73:130–134.

MacLean PD, Horwitz NH, Robinson F. Olfactory-like responses in pyriform area to non-olfactory stimulation. *Yale J. Biol. Med.* 1952;25:159–172.

McGaugh JL. Memory consolidation and the amygdala: a systems perspective. *Trends Neurosci.* 2002;25:456.

McGaugh JL. The amygdala modulates the consolidation of memories and emotionally arousing experiences. *Ann. Rev. Neurosci.* 2004;27:1–28.

McGinty JF. Advancing from the ventral striatum to the extended amygdala. Implications for neuropsychiatry and drug abuse. Introduction. *Ann. NY Acad. Sci.* 1999;877:xii-xxv.

Moss H, Damasio AR. Emotion, cognition, and the human brain. *Ann. NY Acad. Sci.* 2001;935: 98–100.

Nauta W, Feirtag M. *Fundamental Neuroanatomy.* New York: Freeman; 1986.

Olds J, Milner P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J. Comp. Physiol. Psychol.* 1954;47:419–427.

Papez JW. A proposed mechanism of emotion. *J. Neuropsychiatry Clin. Neurosci.* 1995;7:103–112 (reprint of 1937 article).

Rolls ET. *The Brain and Emotion.* New York: Oxford University Press; 1999.

Schachter S. *The Interaction of Cogniitive and Physiological Determinants in the Emotional State.* In: Berkowitz L, ed. New York: Academic; 1994:49–80.

Scoville WB, Milner B. Loss of Recent Memory After Bilateral Hippocampal Lesions. *J. Neurochem.* 1957;20:11–21.

Sica AL, Ruggiero DA, Hundley BW, Gootman PM. The sympathetic nervous system of the developing mammal. In: Scharf SM, Pinsky, Michael R, Magder S, eds. *Respiratory–Circulatory Interactions in Health and Disease.* New York: Marcel. Dekker; 2001; 145–181.

Swanson LW. The amygdala and its place in the cerebral hemisphere. *Ann. NY Acad. Sci.* 2003;985:174–184.

Tzschentke TM, Schmidt WJ. Functional relationship among medial prefrontal cortex, nucleus accumbens, and ventral tegmental area in locomotion and reward. *Crit. Rev. Neurobiol.* 2000;14:131–142.

Vogt BA, Gabriel M, eds. *Neurobiology of Cingulate Cortex and Limbic Thalamus: A Comprehensive Handbook.* Boston: Birkhäuser; 1993.

Webster JI, Tonelli L, Sternberg EM. Neuroendocrine regulation of immunity. *Annu. Rev. Immunol.* 2002;20:125–163.

Weinberger DR, Berman KF, Suddath R, Torrey EF. Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: a magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. *Am .J. Psychiatry* 1992;149:890–897.

23 Thalamus

Modulation of Thalamic Activity
Morphologic and Functional Aspects
Neurons and Nuclei of the Thalamus
Nuclei of the Thalamus: Major Connections and Functions
Limbic Thalamus
Thalamic Neurotransmitters
Extrathalamic Modulatory Pathways Projecting to the Cerebral Cortex
Internal Capsule
Functional Considerations
Lesions of the Thalamus

The *thalamus*, also called the *dorsal thalamus*, is a large, paired, egg-shaped mass of nuclei located in the diencephalon (*see* **Figs. 23.1 to 23.3**). It is bounded rostrally by the interventricular foramen, dorsally by the transverse cerebral fissure, ventrally by the hypothalamic sulcus, and posteriorly by the posterior commissure, at the midline (*see* **Figs. 1.5 and 5.1**). Lateral to the midline, it extends further back to overlap the midbrain (*see* **Fig. 13.16**). Thalamic nuclei *process*, *integrate,* and relay information for the sensory, motor, limbic, and motivational systems. Some play a critical role in sensation and motor control. Thalamic nuclei also appear important for transferring information from one part of the cerebral cortex to another. The thalamus is so strongly interrelated with the cerebral cortex that in some senses, it can be regarded as the deepest layer of the cortex (Sherman and Guillery, 2001). Activity of thalamic nuclei is regulated by input from ascending and related pathways, the cerebral cortex, and the thalamic reticular nucleus.

MODULATION OF THALAMIC ACTIVITY

Drivers and Modulators

The terms first, second, and third order generally are used to denote a sequence of fibers in a sensory pathway. The cell body of a first-order neuron usually is in the peripheral nervous system dorsal root or cranial nerve ganglion. By convention, second-order neurons usually project to the thalamus and third-order project from the thalamus to the cortex. The term first order also is used in a different context; "*first-order relay*" refers to a thalamic nucleus that relays or transmits "driver inputs" from sensory pathways, cerebellum, and basal ganglia to the cerebral cortex for the first time. They drive the cortex. These *thalamic relay nuclei* also are the sites of reciprocal input from layer 6 of the cortex. This reciprocal input, referred to as "*modulatory input,*" can change the pattern of transmission, but not significantly alter its essential characteristics. Thalamic *association*

nuclei do not receive input from major ascending tracts or extrathalamic sources like the cerebellum or basal ganglia. Instead, these nuclei receive major "*driver input"* from layer 5 of the cortex and relay information back to other cortical areas. Referred to as "*higher-order relays,*" they also get modulatory input from layer 6 of the cerebral cortex. Higher-order thalamic nuclei are considered important for modulating signals transferred bidirectionally between different parts of the cortex. In addition, there is direct cortico-cortical communication. It is thought that a thalamic neuron receives more modulatory input than driver input and that the former may activate slower acting metabrotropic receptors, whereas the driver input activates the more rapid ionotropic receptors. There are conformational differences in the synapses of drivers and modulators related to their respective functions.

Thalamic Reticular Nucleus

The *reticular nucleus of the thalamus* is a thin, two- to three-neuron thick shield located within the fascicles of the external medullary lamina just medial to the posterior limb of the internal capsule (*see* **Fig. 23.1**). Its major function is to modulate the activity of the other thalamic nuclei. Although derived from the ventral thalamus, it is considered together with the dorsal thalamus because of intimate anatomic and functional relationships. The thalamic reticular nucleus is neither anatomically nor functionally related to the brainstem reticular formation. The input to the reticular nucleus is derived from (1) collaterals of thalamocortical axons projecting from the other nuclei of the thalamus to the cortex and (2) axon collaterals of corticothalamic fibers. The outputs of its neurons are via (a) long axons that extend medially into the thalamus and (b) short axons terminating within the nucleus itself. Neurons in localized parts of the reticular nucleus project back to the nearby thalamic nucleus from which each receives input. The thalamic reticular nucleus does not project directly to the cerebral cortex. Its neurons are GABAergic. The nucleus has a high concentration of nicotinic cholinergic receptors, which are sensitive to acetylcholine.

The role of the inhibitory GABAergic neurons of the reticular nucleus is to modulate, integrate, and "gate" activities and to regulate transmission of the thalamic nuclei that project to the cerebral cortex. This is accomplished through afferent connections that enable its neurons to sample the activity of the axons passing from the thalamus to the cortex and from the cortex to the thalamus, and via its efferents. These terminate directly on thalamic projection neurons as well as on GABAergic interneurons, which constitute up to 25% of the thalamus. The interneurons, in turn, inhibit the thalamic projection neurons. Thus, the thalamic reticular nucleus directly inhibits the neurons that project to the cortex while providing some excitation by inhibiting the interneurons, allowing for very subtle modulatory effects. The thalamic reticular nucleus also exerts influence on the basal ganglia (Chap. 24). This occurs through interaction with collaterals of both the thalamostriatal fibers from the

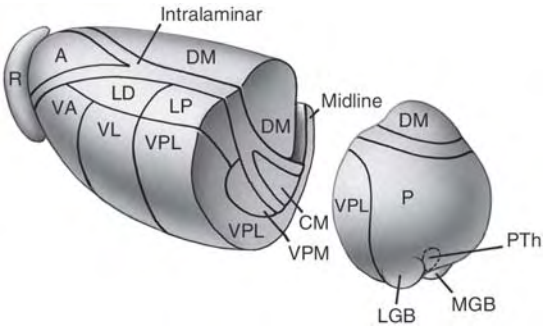


Figure 23.1: The left thalamus. The reticular nucleus (R) extends along the lateral aspect of the thalamus; only its rostral portion is shown. A, anterior nuclear group; CM, centromedian nucleus; DM, dorsomedial nucleus; LD, lateral dorsal nucleus; LGB, lateral geniculate body; MGB, medial geniculate body; P, pulvinar; PTh, posterior thalamic nucleus; VA, ventral anterior nucleus; VL, ventral lateral nucleus; VPL, ventral posterior lateral nucleus; VPM, ventral posterior medial nucleus. Not shown: ventral posterior inferior nucleus.

intralaminar nuclei and reciprocal pallidothalamic fibers from the globus pallidus (Chap. 24).

MORPHOLOGIC AND FUNCTIONAL ASPECTS

The thalamus is located between the third ventricle medially and the posterior limb of the internal capsule laterally (*see* **Fig. 1.8**). The *thalamic reticular nucleus* (R) forms a thin sheet of cells covering its entire lateral side and rostral pole (*see* **Fig. 23.1**). The thalamus consists of several groups of nuclei. Although different sources present slight variations in this regard, the individual nuclei have consistent designations. The diagonally oriented *internal medullary lamina*, a complex of nuclei and fibers, separates the thalamus into a medial group toward the midline and two tiers of nuclei laterally, which form the ventral and lateral groups. The ventral group includes the *ventral anterior* (VA), *ventral lateral* (VL), *ventral medial* (VM), and *ventral posterior nuclei* (VP) (*see* **Table 23.1**). The *medial geniculate body* (MGB) and *lateral geniculate body* (LGB) are caudal extensions of the ventral group; some authors place them separately. The lateral group comprises the *lateral dorsal nucleus* (LD), *lateral posterior nucleus* (LP), and the *pulvinar* (P). The medial group consists of the *dorsomedial nucleus* (DM) (or *mediodorsal nucleus*). The *anterior nuclear group* (A) is in the rostral thalamus between the bifurcated fibers of the internal medullary lamina. The intralaminar nuclear group is within the internal medullary lamina; one of these nuclei, the *centromedian* (CM) is illustrated in **Fig. 23.1**. The midline group, also known as the *periventricular nuclei,* are on the medial surface of the thalamus and in the massa intermedia (absent in 30% of human brains), which spans the third ventricle. Some nuclei have subdivisions, which could have distinct connections.

All thalamic nuclei receive afferent input from at least one extrathalamic source: (1) The greatest input is from the cerebral cortex with which all, except the thalamic reticular nucleus, have reciprocal connections. (2) All influences received by the cerebral cortex are derived from thalamic nuclei, with two exceptions: pathways of the olfactory system (Chap. 14) and extrathalamic modulatory pathways. (3) Interconnections between thalamic nuclei, if any, are scarce. Exceptions are extensive interconnections between various intralaminar nuclei and with the reticular nucleus.

On a functional basis, thalamic nuclei can be classified as *relay, association,* or as *diffuse-projecting nuclei* (*see* **Table 23.1**). (1) Each relay nucleus is associated with a distinct sen-

Table. 23-1:
Organization of Thalamic Nuclei

Relay Nuclei (First Order)
Anterior Nuclear Group (A)
Anteroventral nucleus
Anterodorsal nucleus
Anteromedial nucleus
Medial Nuclear Group
Dorsomedial nucleus (DM) or mediodorsal
Ventral Nuclear Group
Ventral anterior nucleus (VA)
Ventral lateral nucleus (VL)
Ventral posterior nucleus (VP)
Ventral posterior lateral (VPL)
Ventral posterior medial (VPM)
Ventral posterior inferior (VPI)
Medial geniculate body (MGB)
Lateral geniculate body (LGB)
Posterior Nuclear Group
Posterior thalamic nucleus (PTh)
Ventral medial nucleus (VM)
Association Nuclei (Higher Order)
Lateral Nuclear Group
Laterodorsal nucleus (LD
Lateral posterior nucleus (LP)
Pulvinar (P)
Diffuse Projecting Nuclei
Intralaminar Nuclear Group
Rostral—central medial, central lateral
Caudal—centromedian (CM), parafascicular (Pf)
Midline Nuclear Group
Thalamic Reticular Nucleus*

*Does not project to the cerebral cortex.

sory modality or with an input derived from a subdivision of the motor or limbic system. These nuclei match the definition of "drivers." Projections from a relay nucleus terminate topographically in a cytoarchitecturally or functionally defined region (field) of the cerebral cortex. In turn, each thalamic nucleus receives a massive projection from layer 6 of the same cortical field to which it projects. These recurrent projections are presumed to enable the cortex to modulate the input relevant to ongoing activity. The cortex receives "driver" signals from the relay nuclei and the latter receives "modulator" connections from the cortex. (2) Similar to relay nuclei, association nuclei have reciprocal topographic connections with the cortex, but the cortical input is from layer 5 as well as from layer 6. Because this is the first time the association nuclei get major input, it is regarded as "driver" input. This distinction is not total in all cases. (3) The diffuse-projecting nuclei have widespread connections with neurons in other nuclei and the cortex. They exert influences that affect the activity of the neurons in the thalamus and cerebral cortex. They have a role in governing the level of arousal. (4) Fibers projecting (a) from the thalamus to the cortex and (b) from the cortex to the thalamus pass through the internal capsule and corona radiata (*see* **Figs. 23.2 and 13.5**).

NEURONS AND NUCLEI OF THE THALAMUS

The major thalamic nuclei contain two basic types of neuron: projection neurons and interneurons. Projection neurons arising from relay and association nuclei have a large axon that goes to layer 4 of the cerebral cortex; each axon has collaterals that terminate in the reticular nucleus. The interneurons have axons that terminate locally within the same nucleus. They are concerned with information processing within the nucleus.

Functionally, thalamic nuclei and their projections are called specific or nonspecific. *Specific thalamic nuclei* are characterized as having reciprocal topographic connections with localized areas of the cerebral cortex. Depending on the author, these are restricted to those nuclei associated with sensory and motor systems, or to all of the relay and association nuclei. *Nonspecific thalamic nuclei* are characterized as receiving input from the brainstem reticular formation, other thalamic, and basal forebrain nuclei and sending their output to widespread areas of the cerebral cortex as well as to the striatum. These comprise the midline and intralaminar thalamic nuclei. The thalamic reticular nucleus also is classified as nonspecific, although it emits no projections to the cortex.

To summarize, each cortical area receives both specific and nonspecific thalamocortical projections. The restricted specific projection arises from a thalamic relay or association nucleus and diffuse nonspecific projections from other thalamic (and even extrathalamic) sources including parts of specific relay nuclei, diffuse projecting thalamic nuclei, and nuclei outside of the thalamus.

NUCLEI OF THE THALAMUS: MAJOR CONNECTIONS AND FUNCTIONS

Major nuclei of the thalamus are illustrated in **Figs. 23.3** and **23.4** and listed in **Table 23.1**. Subdivisions are discussed only insofar as they are mentioned in other chapters.

Anterior Nuclear Group

The anterior group comprises the *anteroventral*, *anterodorsal,* and *anteromedial nuclei*, which form the *anterior thalamic tubercle*. They are major components of the *limbic thalamus* and are integrated in the *Papez circuit* and limbic system (Chap. 22). The anterior nuclei contain the highest concentration of muscarinic receptors of the thalamus. They have reciprocal connections with the (1) hypothalamus, particularly the mammillary body via the *mamillothalamic tract*, (2) hippocampal formation in

the temporal lobe via the *fornix*, (3) cingulate gyrus of the limbic lobe, and (4) the prefrontal cortex. The latter is the neocortical component of the limbic system.

Medial Nuclear Group (Dorsomedial Nucleus)

The massive *dorsomedial nucleus* (DM) located between the internal medullary lamina and the third ventricle is divided into a *magnocellular (large cell) portion* and a *parvocellular (small cell) portion*. Its principal inputs are from the amygdala, olfactory system, and hypothalamus and its primary output is to the prefrontal lobe. In primate evolution, the relative increase in size of this nucleus parallels that of the frontal lobe. The nucleus has rich connections with the intralaminar nuclei, nuclei of the midline, and the lateral posterior thalamic nucleus. The magnocellular portion has reciprocal connections with the amygdala, lateral hypothalamus, and the temporal and orbitofrontal neocortex. The parvocellular portion has massive topographically organized reciprocal connections with the prefrontal cortex (areas 8, 9, 10, 11, and 12—all rostral to area 6; Chap. 25). A point-to-point relation exists among areas in the amygdala, DM and frontal lobe. The DM nucleus has massive reciprocal connections with the *frontal eye field* (area 8). The ventral caudal part of the nucleus (DMvc), involved in mechanisms of pain, receives inputs from the spinothalamic and anterior trigeminothalamic tracts and projects

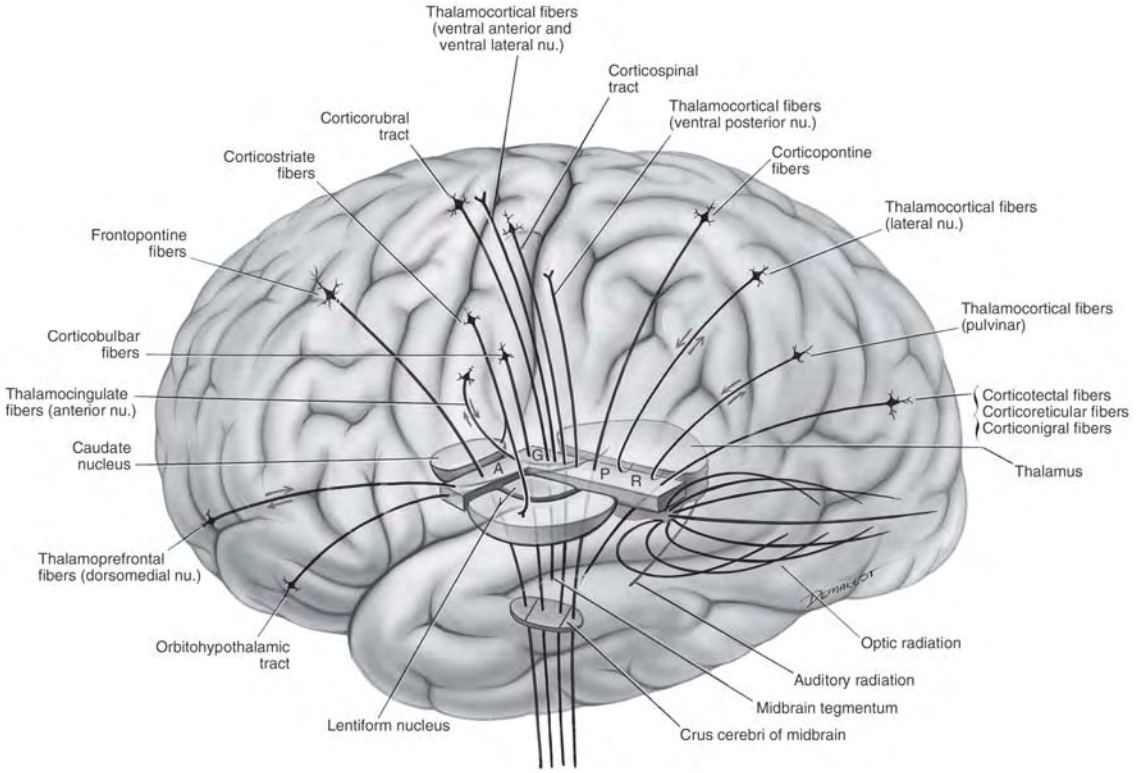


Figure 23.2: Some component fiber tracts of the internal capsule (shown in horizontal plane) and their cortical connections. Reciprocal projections between a thalamic nucleus and a cortical area are indicated by arrows pointing in two directions. A, anterior limb; G, genu; P, posterior limb; R, retrolenticular portion of posterior limb of internal capsule.

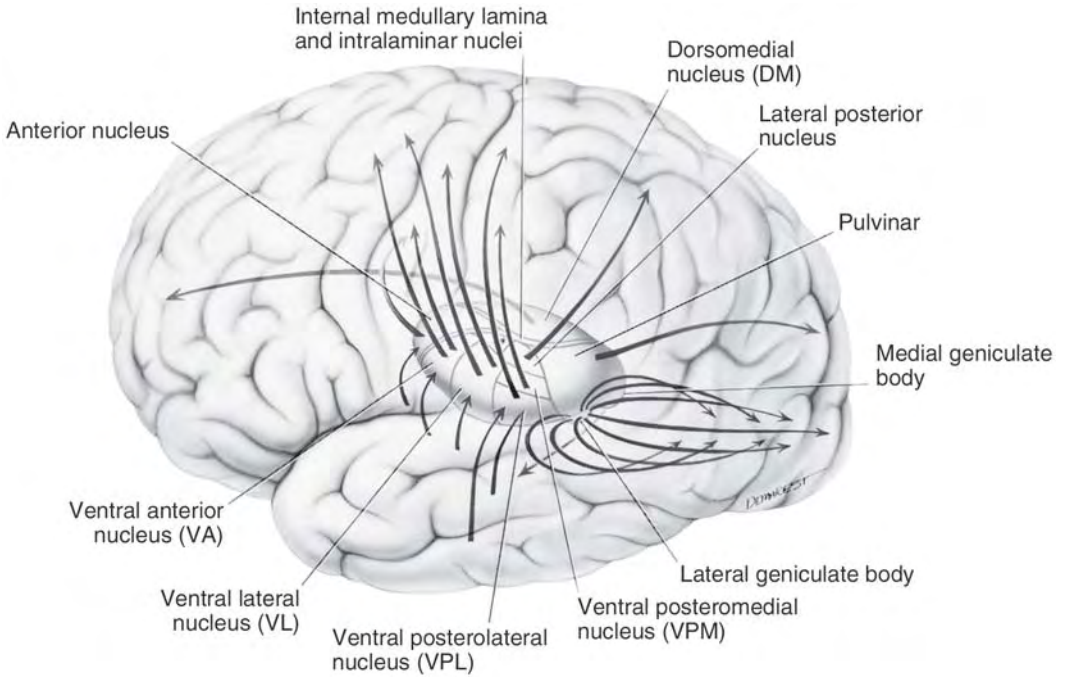


Figure 23.3: Major nuclei and some major cortical projections of the thalamus. Thalamic nuclei generally have reciprocal connections (corticothalamic projections indicated by arrows) with the cortex. The medial geniculate body projects to auditory areas 41 and 42, the lateral geniculate body projects to visual area 17, the VPM nucleus projects to the sensory postcentral gyrus (face region of areas 1, 2, and 3) and secondary sensory area, the VPL nucleus projects to the sensory postcentral gyrus (body region of areas 1, 2, and 3) and secondary sensory area, the VL nucleus projects to motor areas 4 and 6, the VA nucleus projects to motor areas 6 and 8 and orbitofrontal cortex, the anterior nucleus projects to the cingulate gyrus, the lateral posterior nucleus and pulvinar projects to the association cortex of the parietal, occipital, and temporal lobes, and the dorsomedial nucleus projects to prefrontal cortex.

to the part of the cingulate gyrus adjacent to the rostrum of the corpus callosum (Chap. 9). Thus, DM, although largely an association nucleus, has a subdivision that conforms to the definition of a relay nucleus.

The DM nucleus acts to integrate certain influences from somatic and visceral sources and, in conjunction with the prefrontal cortex, has roles in various expressions of affect, emotion, and behavior. Psychosurgical studies, such as following prefrontal lobotomy or leukotomy (Chap. 25), indicate that the DM nucleus and the frontal lobe cortex are involved with affective behavior.

Ventral Nuclear Group

The ventral nuclear group comprises the ventral anterior, ventral lateral and ventral posterior nuclei, as well as the medial and lateral geniculate bodies, which are a caudal extension.

Ventral Anterior Nucleus. The ventral anterior (VA) and ventral lateral *thalamic nuclei* are motor relay nuclei associated with the somatic motor system. The VA nucleus is divided into two subdivisions: (1) parvocellular (principal) part (VApc) and (2) magnocellular part (VAmc). Each part receives input from different sources without overlap. VApc receives

afferents from the medial segment of the globus pallidus and VAmc receives afferents from the pars reticulata of the substantia nigra. VA projects selectively to the supplementary motor area (SMA, area 6) (*see* **Fig. 25.3** and Chap. 24). Premotor cortical area 6 projects primarily to VApc and area 8 projects to VAmc. Fibers from the primary motor cortex do not terminate in the VA nucleus. Nonspecific input from the intralaminar nuclei to the "nonspecific portion" of VA are processed and projected to the orbitofrontal cortex.

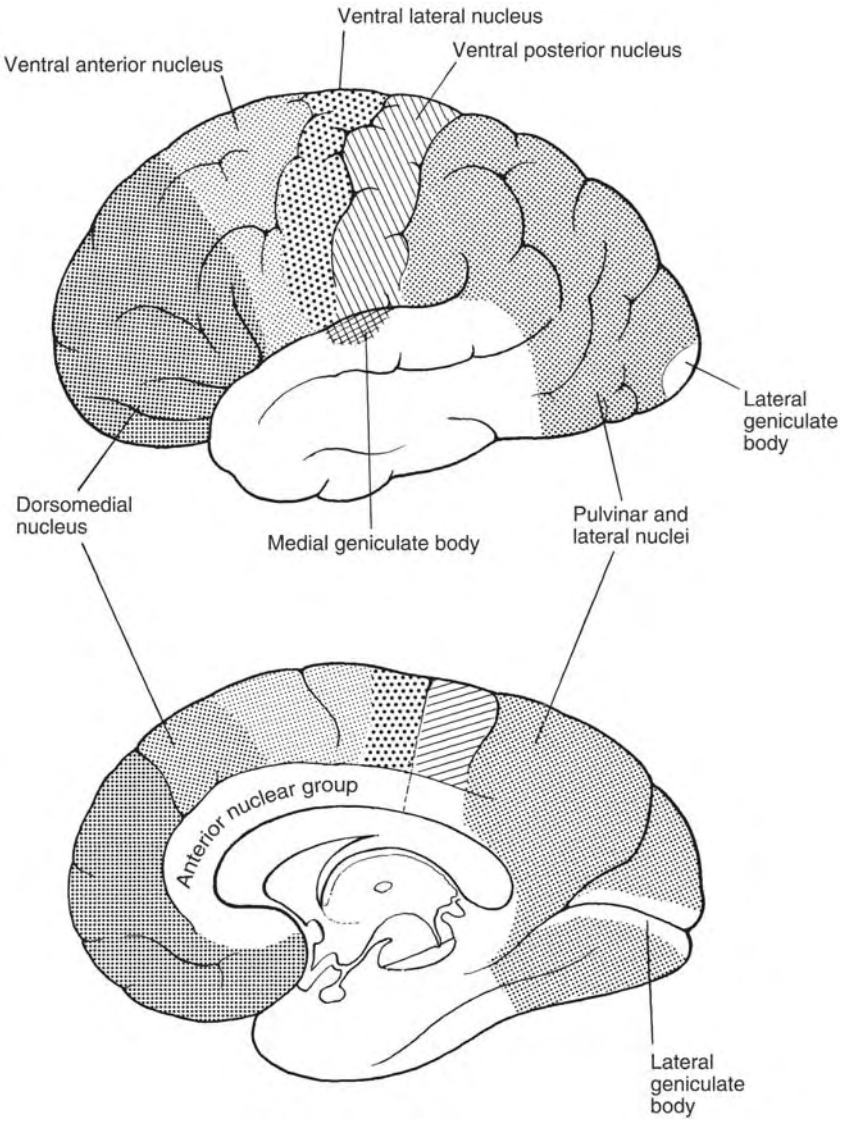


Figure 23.4: Lateral and medial views of the left cerebral hemisphere illustrating cortical projection areas of some thalamic nuclei. Much of the temporal lobe does not receive projections from the specific thalamic nuclei. Such an area is known as the athalamic cortex.

Ventral Lateral Nucleus. The ventral lateral nucleus (VL) is an integral nucleus in the feedback circuits of (1) cerebral cortex to cerebellar cortex back to cerebral cortex (*see* **Fig. 18.4**) and (2) cerebral cortex to basal ganglia to cerebral cortex (*see* **Figs. 24.5 and 24.6** and Chaps. 18 and 24). The VL nucleus receives direct input from the contralateral cerebellar hemisphere via the dentatothalamic tract (specifically from globose, emboliform, and dentate nuclei) (Chap. 18). It also receives input from the medial segment of the ipsilateral globus pallidus. There is apparently no overlap of the termination of the input from the cerebellum and globus pallidus (Chap. 24). The portion of VL receiving input from the cerebellum projects to the premotor cortex (part of area 6) and to the primary motor cortex (area 4; Chap. 25). The connections with area 4 are *somatotopically* and *reciprocally organized* with (1) the medial region of VL interconnected with the cortical face area, (2) the intermediate region interconnected with the upper limb and body area, and (3) the lateral region interconnected with the pelvis and lower limb area. The portion of VL receiving input from the globus pallidus projects to the supplementary motor area (portion of area 6) (Chap. 25). Through its projections to the cortex, VL exerts its role as a critical subcortical gateway to the cerebral cortex acting as a prime mover in the motor pathways (Chap. 24). Lesions in the VL might ameliorate the contralateral tremors and rigidity in patients with Parkinson's disease (Chap. 24).

Ventral Posterior Nucleus. The ventral posterior nucleus (VP) of the *ventrobasal complex* is a somatosensory relay nucleus divided into *ventral posterolateral* (VPL), *ventral posteromedial* (VPM), and *ventral posteroinferior* (VPI) nuclei. The VP is highly organized with a precise topographical representation and separation of the sensory modalities of the contralateral half of the head and body (Chaps. 9 and 10).

The ventral posterior nucleus is the nucleus of termination of somatosensory and gustatory pathways. The VPL and VPI are nuclei of termination of the lateral spinothalamic tract (pain and thermal sense from the body), medial lemniscus ("pressure" touch and vibratory sense from the body), anterior spinothalamic tract (light touch from the body), and spinocervicothalamic tract (touch, proprioception, and vibratory sense from the body). In addition, the VPI is a nucleus of the vestibular pathway (Chap. 16). The VPM is the nucleus of termination of the trigeminothalamic tracts (general sensory modalities of the head) and of the gustatory pathways from the nucleus solitarius. A somatotopic distribution in the VPL is represented as follows: The pathways from the lower extremity terminate posterolaterally and from the upper extremity anteromedially, with fibers from the body in between. The different modalities also are topographically localized within the VPM: (1) taste is projected to the medial portion of the nucleus, (2) tactile sense is projected to the lateral portion, and (3) thermal sense is projected to the intermediate portion. The topographic and sensory modality organization is preserved in the thalamocortical projections. The projections terminate in the primary somatic sensory cortex (SI, areas 3, 1, and 2) and the secondary somatic sensory cortex (SII) (Chap. 25). The entire body is represented in the VPI.

Medial Geniculate Body. The medial geniculate body (MGB) is a nucleus in the auditory pathways that receives its main afferent input from the inferior colliculus via the brachium of the inferior colliculus. These ascending fibers terminate in the appropriate isofrequency laminae, resulting in a highly ordered bilateral tonotopic projection of the cochlea within the MGB. This tonotopic organization is projected via geniculocortical fibers to the tonotopically organized primary auditory cortex, where high pitch tones are localized medially and low tones laterally (area 41 and 42; Chap. 16).

Lateral Geniculate Body. The lateral geniculate body (LGB) is a six-layered nucleus that (1) receives input from the retina of both eyes via the optic tract and (2) has reciprocal con-

nections via the geniculocalcarine tract (optic radiations) with the primary visual cortex (VI, area 17). The LGB has two critical functional roles: (1) the precise transmission of visual input from the retina to the primary visual cortex and (2) the modulation and regulation of the flow of visual information to the primary visual cortex. The latter expressions involve the extensive corticogeniculate projections from area 17 to the LGB. These are integrated into feed-forward and feedback inhibitory circuits (Chap. 3), which process "visual" information and regulate its flow. These connections are thought to be involved in arousal, in regulating the level of visual attention, and in modulating the flow of information to area 17.

Posterior Nuclear Group

The posterior nuclear group consists of several nuclei caudal to the ventrobasal complex that include the *posterior thalamic nucleus* (PTh) (*see* **Fig. 23.1**), the *ventral medial nucleus* (VM), and other nuclei not relevant here. The input to PTh is derived from diverse sensory sources including the spinothalamic tracts, trigeminothalamic tract, medial lemniscus, inferior colliculus and ascending reticular pathways. Its neurons are multimodal rather than modality specific, in that they respond to combinations of pain, tactile (mechanoreceptive), vestibular, and auditory stimuli. Physiologically, the neurons of this nucleus respond to high-threshold somatic sensory and auditory stimuli and have properties consistent with an involvement in central nervous system pain mechanisms. The PTh nucleus projects to the secondary somatic sensory area of the cerebral cortex (Chap. 25). It is thought to have a role in the perception of pain and noxious stimuli. The posterior part of VM, not illustrated, receives profuse terminals from the spinothalamic tract and projects to the anterior end of insula cortex. It also is important in mechanisms of pain perception.

Lateral Nuclear Group

The lateral nuclear group, located dorsal to the ventral group of nuclei, is comprised of the lateral dorsal, lateral posterior, and pulvinar nuclei (*see* **Fig. 23.1**). These are classified as association nuclei.

Lateral Dorsal Nucleus. The lateral dorsal nucleus (LD) is a part of the limbic thalamus; it is actually a caudal extension of the anterior nuclear group. It has reciprocal connections with the posterior cingulate gyrus and parahippocampal gyrus. It also receives input from the septal area. The lateral dorsal nucleus might be involved in emotional expression exhibited by the limbic system.

Lateral Posterior Nucleus and the Pulvinar. The lateral posterior nucleus (LP) is considered to be a rostral extension of the massive pulvinar (P) (*see* **Fig. 23.1**). The LP and the pulvinar receive significant afferent input from nuclei associated with the visual system such as the superior colliculus and the pretectal nuclei. They are presumed to have a role in the processing of directed visual attention. Both nuclei have reciprocal connections with areas 5 and 7 of the posterior parietal cortex and the pulvinar with widespread portions of the temporal lobe as well. The projection field of the pulvinar sometimes is referred to as the parieto–temporo–occipital association cortex.

Intralaminar Nuclear Group

The intralaminar nuclei are structurally and functionally rostral extensions of the brainstem reticular formation into the diencephalon. They are extensively interconnected with each other. Frequently, they are divided into rostral and caudal nuclei, as shown in **Table 23.1**.

Afferent input is derived from the brainstem reticular formation, substantia nigra, superior colliculus, pretectum, and spinothalamic tract (pain). The deep cerebellar nuclei project to the intralaminar nuclei, with the exception of the parafascicular nucleus (Pf). The central medial and Pf nuclei receive afferents from the globus pallidus of the basal ganglia. The Pf and central lateral nuclei receive input from the spinothalamic tract.

The intralaminar nuclei have rich projections to both the putamen and caudate nucleus

of the striatum and to widespread areas of the cerebral cortex, where the fibers are distributed to all, but particularly, the superficial layers. All intralaminar nuclei have reciprocal interconnections with the cerebral cortex. (1) A triangular relation exists among defined regions of the cerebral cortex, intralaminar nuclei, and striatal nuclei. From a common cortical area, corticothalamic fibers project to defined regions of the intralaminar nuclei and corticostriatal fibers project to the striatum. To complete the triangle, intralaminar–striatal projections interconnect the same regions of the intralaminar nuclei and the striatum. (2) Each of the intralaminar nuclei has diffuse and reciprocal thalamocortical projections to wide areas of the cerebral cortex. The central medial nucleus projects to rostral portions of the frontal lobe, including the limbic areas and cingulate gyrus. The Pf nucleus projects to the lateral and rostral areas of the frontal lobe. The centromedian nucleus has copious projections to the premotor and motor areas, and the central lateral nucleus has projections to the somatic sensory areas, related parietal areas, and visual association areas of the occipital cortex.

The intralaminar nuclei have several roles. Their widespread cortical projections are involved with the maintenance of arousal, which is integral to the general state of awareness. Their connections to the somatic sensory areas of the cortex indicate a role in sensorimotor integration. The direct spinothalamic, trigeminothalamic and multisynaptic thalamic pain pathways do have some terminal connections in these nuclei and presumably have a role in arousal and/or in pain perception.

Midline (Periventricular) Nuclear Group

The midline nuclei are a thin band of nuclei adjacent to the third ventricle. Dorsal midline nuclei have connections with both the striatum and the limbic cortex (e.g., prefrontal lobe). Thus, the midline nuclei and intralaminar nuclei are similar in that they have topographic projections to both the cerebral cortex and striatum. Ventral nuclei have connections with the hippocampal region. Brainstem reticular neurons project ascending adrenergic and serotonergic fibers to the midline nuclei. A role in visceral activities has been presumed.

LIMBIC THALAMUS

The limbic thalamus is generally defined as the nuclei of the thalamus that have connections with limbic lobe cortex and, in particular, with the cingulate gyrus (Chap. 22). These include the anterior nuclear group of the thalamus and portions of some other thalamic nuclei. Area 24 of the cingulate gyrus is a major projection site of the anterior nuclear group (*see* **Fig. 25. 6**). Areas 25, 29, and 32 also receive input from this group. Other thalamic nuclei with some connections to the cingulate gyrus include the dorsomedial, lateral dorsal, lateral posterior, pulvinar, and the intralaminar nuclei. The limbic thalamus is conceived as having a role in visceral emotions, the visceral aspects of behavior and even in learning and memory.

THALAMIC NEUROTRANSMITTERS

The inhibitory transmitter GABA and the excitatory transmitters glutamate and possibly aspartate are associated with the thalamus (Chap. 15). GABAergic neurons include virtually all cells of the thalamic reticular nucleus and interneurons within the thalamic nuclei. In addition, GABA is released by axons of neurons of the globus pallidus and substantia nigra that terminate in the ventral anterior and ventral lateral nuclei. The inhibitory interneurons in the sensory relay nuclei presumably contribute to the enhancement of stimulus contrasts by lateral inhibition (Chap. 3) and, thus, the selection of certain types of stimulus and the suppression of others (Chaps. 9 and 10). The GABAergic neurons of the reticular nucleus, as noted earlier, "gate" the thalamic activity projected to the cerebral cortex.

Glutamate is the major neurotransmitter released by thalamic neurons projecting to the

cortex as well as by the massive corticothalamic projections.

EXTRATHALAMIC MODULATORY PATHWAYS PROJECTING TO THE CEREBRAL CORTEX

The *extrathalamic modulatory pathways* comprise systems that arise from cholinergic and monoaminergic nuclei located primarily in the brainstem and the basal forebrain. They project, without any relays in the thalamus, directly to the cerebral cortex, where they exert modulatory control over the excitability level of the cortical neurons. They have roles in relation to wakefulness, arousal, and the phases of sleep.

The *serotonergic pathway* originates in the raphe nuclei located in the midbrain and rostral pons (Chap. 15). They could be involved with sleep and pain control. The *noradrenergic pathway* originates in the locus ceruleus. These neurons are actively releasing norepinephrine during arousal and situations of attention and extreme vigilance. The *dopaminergic pathway* arises in neurons of the ventral tegmental area and terminates in all areas of the cortex. The densest projections are to the motor cortex. The *cholinergic* and *GABAergic pathways* originate respectively from the basal nucleus of Meynert and associated nuclei in the basal forebrain. The cholinergic neurons of the basal nucleus project to the cerebral cortex and the GABAergic nucleus from the basal forebrain to the hippocampus. Changes in these acetylcholine terminals of the cortex might contribute in some degree to the dementia of Alzheimer's disease. They have a role in cortical arousal. The *histaminergic pathway* (histamine) arises from neurons in the lateral hypothalamus and terminates in all areas of the cortex.

Nuclei of the brainstem reticular formation and basal forebrain have axons that terminate in the intralaminar thalamic nuclei; the latter, in turn, have diffuse projections terminating in all areas of the cortex. Thus, the monoaminergic and cholinergic pathways exert continuous modulatory influences on thalamic and cortical neurons and the resultant behavioral state (sleep–wake) of the individual.

INTERNAL CAPSULE

The internal capsule is one portion of a continuous massive sheet of fibers projecting to and projecting from the cerebral cortex. The sheet extends as the *crus cerebri* of the midbrain, the *internal capsule* of the diencephalon, and the *corona radiata* of the cerebral white matter to the cerebral cortex (Chap. 1; **Figs. 1.8, 13.4, 13.5, and 23.3**). The fibers of the internal capsule convey almost all of the neural input to and output from the neocortex (Chap. 25); they are the direct lines of communication with the subcortical nuclei, especially the thalamus, brainstem and spinal cord. The internal capsule is subdivided into an anterior limb located between the head of the caudate nucleus and the lenticular nucleus, the genu located at the bend (genu) between the anterior and posterior limbs, and a posterior limb located between the thalamus and the lenticular nucleus and extending behind it (retrolenticular portion of the posterior limb) (*see* **Figs. 1.8 and 23.2**).

The fibers passing through the *anterior (caudatolenticular) limb* of the internal capsule include (1) frontopontine fibers to nuclei in the pons, (2) corticostriate fibers to the striatum, and the following pathways composed of reciprocal connections of fibers between (3) the prefrontal cortex and the dorsomedial thalamic nucleus, (4) the cingulate gyrus and the anterior thalamic nucleus, and (5) the septal area and the hypothalamus (medial forebrain bundle).

The *genu* of the internal capsule contains corticobulbar and corticoreticular fibers.

The *posterior (thalamolenticular) limb* is composed of both motor pathways and sensory pathways. Through the rostral half of this limb pass the corticospinal, corticorubral, and corticoreticular tracts. Through the caudal half of this limb pass thalamocortical projections from the ventral anterior, ventral lateral, and ventral posterior thalamic nuclei.

The *retrolenticular (postlenticular) portion* of the posterior limb is composed of optic (geniculocalcarine) radiation, auditory (geniculotemporal) radiation, and corticopontine fibers from the temporal, parietal, and occipital cortices.

FUNCTIONAL CONSIDERATIONS

An axiom of thalamic organization is that the nuclei of the dorsal thalamus provide the last subcortical processing stations of the ascending pathways before the resultant information is projected to the neocortex. This might be the initial critical stage in generating each sensory modality into a sensation.

The thalamus is a major neural processor and integrator involved in essentially all activities of the forebrain. All general and special sensory systems, except for the olfactory system, project their major output to the thalamus before the processed information is relayed to the cerebral cortex. The intralaminar nuclei, nuclei of the midline, and part of the ventral anterior nucleus are essential components of the reticular system acting as linkages in the circuitry between the brainstem reticular pathways and the higher centers of the limbic lobe and the neocortex. Thalamic output is the chief source of input to the cerebral cortex; these connections are, to a large degree, integrated into circuits comprising (1) reciprocal connections between thalamic nuclei and the cerebral cortex and (2) circuits among the cortex, basal ganglia, thalamus, and cortex (Chap. 24). The thalamus has a critical role in somatic motor activity through its strategically located nuclei (VA and VL), which receive inputs from the cerebellum and basal ganglia and project influences to the motor cortex (Chaps. 18 and 24).

The thalamus is conceived as being essential for cognition and awareness and can also be critical for arousal. The neuropathological findings in the brain of Karen Ann Quinlan support this view; she was in a persistent vegetative state for 10 years (9 without a respirator)—a condition in which there is wakefulness (arousal) but neither cognition nor awareness. In her case, the most severe damage was not in the cerebral cortex, but in the thalamus. Her brainstem reticular formation was relatively intact.

"Affect" in sensory appreciation is apparently mediated through the thalamic reticular system, dorsomedial nucleus, and anterior nuclear group. The *affect* of an individual relates to his emotional tone and, somewhat, to the phase of the sleep–wake cycle. Well-being, malaise and a state of contentment are expressions of affect. The degree of agreeableness or disagreeableness of any stimulus depends on the state of an individual. The same objective degree of pain, temperature, or touch can evoke a remarkable variety of subjective degrees of reactivities. This variety is an expression of affective sensory mechanisms.

Through the interaction of the nonspecific nuclei and specific nuclei, the thalamus exerts a regulatory drive upon the cerebral cortex. These nuclei act as modulators and modifiers of thalamic processing. In addition, the synchronization and desynchronization of thalamic activity are considered to be dependent, in part, on recurrent collateral branches of thalamic neurons feeding back on interneurons; in turn, these connections modulate the neurons projecting to the cortex. The thalamus is essential to such expressions of synchrony (or desynchrony) as (1) the rhythmic brain wave activity observed in an electroencephalogram and (2) the phasic and tonic movements mediated by the motor pathways. The thalamus is considered to be a "prime mover" of motor pathways. The modulatory effects are exerted in concert with the VL and VA nuclei through (1) the cerebellothalamocortical pathway (Chap. 18) and (2) the globus pallidus–thalamocortical pathway (Chap. 24). Through integrative, modulatory, and synchronizing activities, the thalamus exerts a major effect upon the motor expressions via the cerebral cortex and its projection pathways, including the corticospinal, corticorubrospinal, corticostriate, and corticoreticulospinal tracts, among others.

LESIONS OF THE THALAMUS

Lesions of the thalamus (as a consequence of vascular impairment) can produce signs known as the *thalamic syndrome*. All general somatic modalities can be diminished on the contralateral half of the head and body without complete anesthesia (lesion of ventral posterior nucleus), all general modalities from the face can be normal (the VPM not damaged), tactile sense from the face can be intact (bilateral projections from principal trigeminal nucleus), and some pain and temperature sense on the contralateral side can be retained (these modalities can be bilaterally represented in the thalamus or some qualities of these modalities can be felt in the midbrain). In this syndrome, the threshold for pain, temperature, and tactile sensations is usually raised on the side contralateral to the lesion. In addition to the diminution of sensations, mild stimuli might evoke disagreeable sensations (dysesthesias). The feelings elicited from a pinprick might be an intolerable burning and agonizing pain. Heat, cold, and pressure from one's clothes can be exceedingly uncomfortable. Intractable pain, which does not respond to analgesics, can be a consequence. In response to environmental stimulation, affect qualities are expressions of modified and exaggerated stimuli during emotional stress. For example, the application of a warm object to the hand can evoke a range of feelings from pain to pleasure.

These highly overactive sensory responses are probably the result of alterations in frequencies and patterns of input to the thalamus, irritation of injured neurons, and changes in the quality of the output to the cerebral cortex. In addition, the release from some cortical influences upon the thalamus might be contributory (release phenomena).

A neocerebellar lesion results in cerebellar dyskinesia. This is an expression of a release phenomenon, in which the VL nucleus is released from the normal cerebellar influences relayed rhythmically through the dentatothalamic pathway. Without these influences, the abnormal movements are expressed. The amelioration of cerebellar dyskinesias in man can occur following a surgically placed lesion in the contralateral VL nucleus.

SUGGESTED READINGS

Jones EG. Thalamic circuitry and thalamocortical synchrony. *Phil. Trans. R. Soc. Lond. B. Biol. Sci.* 2002;357:1659–1673.

Jones EG. A pain in the thalamus. *J. Pain.* 2002;3:102–104.

Kinney HC, Korein J, Panigrahy A, Dikkes P, Goode R. Neuropathological findings in the brain of Karen Ann Quinlan. The role of the thalamus in the persistent vegetative state. *N. Engl J. Med.* 1994;330:1469–1475.

Morel A, Magnin M, Jeanmonod D. Multiarchitectonic and stereotactic atlas of the human thalamus. *J Comp Neurol.* 1997;387:588–630.

Price DD, Verne GN. Does the spinothalamic tract to ventroposterior lateral thalamus and somatosensory cortex have roles in both pain sensation and pain-related emotions? *J. Pain.* 2002;3: 105–108.

Sherman SM, Guillery RW. On the actions that one nerve cell can have on another: distinguishing "drivers" from "modulators." *Proc. Natl. Acad. Sci. USA* 1998;95:7121–7126.

Sherman SM, Guillery RW. *Exploring the Thalamus.* San Diego, CA: Academic; 2001.

Sherman SM, Guillery RW. The role of the thalamus in the flow of information to the cortex. *Phil. Trans. R. Soc. Lond. B. Biol. Sci.* 2002;357: 1695–1708.

Treede RD. Spinothalamic and thalamocortical nociceptive pathways. *J. Pain* 2002;3:109–112.

Walker AE. *The Primate Thalamus.* Chicago, IL: The University of Chicago Press; 1938.

Willis WD Jr, Zhang X, Honda CN, Giesler GJ Jr. A critical review of the role of the proposed VMpo nucleus in pain. *J Pain.* 2002;3:79–94.

Zhang L, Jones EG. Corticothalamic inhibition in the thalamic reticular nucleus. *J. Neurophysiol.* 2004;91:759–766.

24
Basal Ganglia and Extrapyramidal System

Organization of the Basal Ganglia
General Circuitry Associated With the Basal Ganglia
Parallel Organization of Functionally Segregated Circuits Linking Basal Ganglia, Thalamus, and Cortex
Side Circuits
Summary
Functional Considerations

The cerebrum exerts control of voluntary somatic motor activity through several descending pathways. The direct pathway is via the pyramidal system, which includes the *corticospinal (pyramidal) tract* together with fibers that diverge from it to innervate cranial nerve motoneurons, the *corticobulbar tract* (*see* **Fig. 24.1**). The cortical neurons that form the tract are upper motoneurons. There are two other major descending pathways that arise from the cortex: the corticorubral/rubrospinal tract and the corticoreticular/reticulospinal tract, but these are less direct. They involve a synapse in the red nucleus and in the reticular formation of the lower brainstem, respectively. Before evolution of the cerebral cortex in mammals, voluntary somatic motor activity was mainly mediated by upper motoneurons in the red nucleus and the brainstem reticular formation. These nuclei together with the corpus striatum, the major component of the basal ganglia and the most important forebrain center for motor control in premammalian vertebrates, were designated as components of the extrapyramidal system whose descending fibers pass through the tegmentum rather than the medullary pyramid. However a dichotomy between a pyramidal and an extrapyramidal system does not really exist. The cortex that gives rise to all of these descending tract systems is anatomically, functionally, and inextricably interconnected with the basal ganglia.

ORGANIZATION OF THE BASAL GANGLIA

The *basal ganglia* are nuclear complexes in the cerebrum and midbrain that play a critical role in the integration of motor activity. Along with the cerebellum, the basal ganglia act at the interface between the sensory and motor systems. The basal ganglia integrate and process afferent input from the cerebral cortex and send the modified signals to the thalamus, which, after further alteration, relays the output back to specific areas of the cerebral cortex. Although this chapter emphasizes the role of the basal ganglia in somatic motor function, this group of nuclei also is of great importance in mechanisms involving emotional and cognitive behaviors. The following information is meant to provide a basic understanding of how the basal ganglia participates in a variety of activities and is a simplification of their functional organization and complex circuitry.

Clinically, resting *movement disorders* (*dyskinesias*), which occur when a patient is not purposefully moving, are generally ascribed to malfunctioning of the basal ganglia. *Parkinson's disease* and *Huntington's chorea*

are two well-known expressions of basal ganglia dysfunction. In order to understand the mechanisms involved, it is important to know the structures that comprise the basal ganglia, fundamentals of the circuitry, and whether the various links excite or inhibit their targets or do both.

The basal ganglia are considered to include the corpus striatum, subthalamic nucleus, substantia nigra, and the ventral tegmental area (*see* **Table 24.1**). This is based on the interrelationships of these structures and their roles in somatic motor function. The pedunculopontine nucleus probably should be added to this list

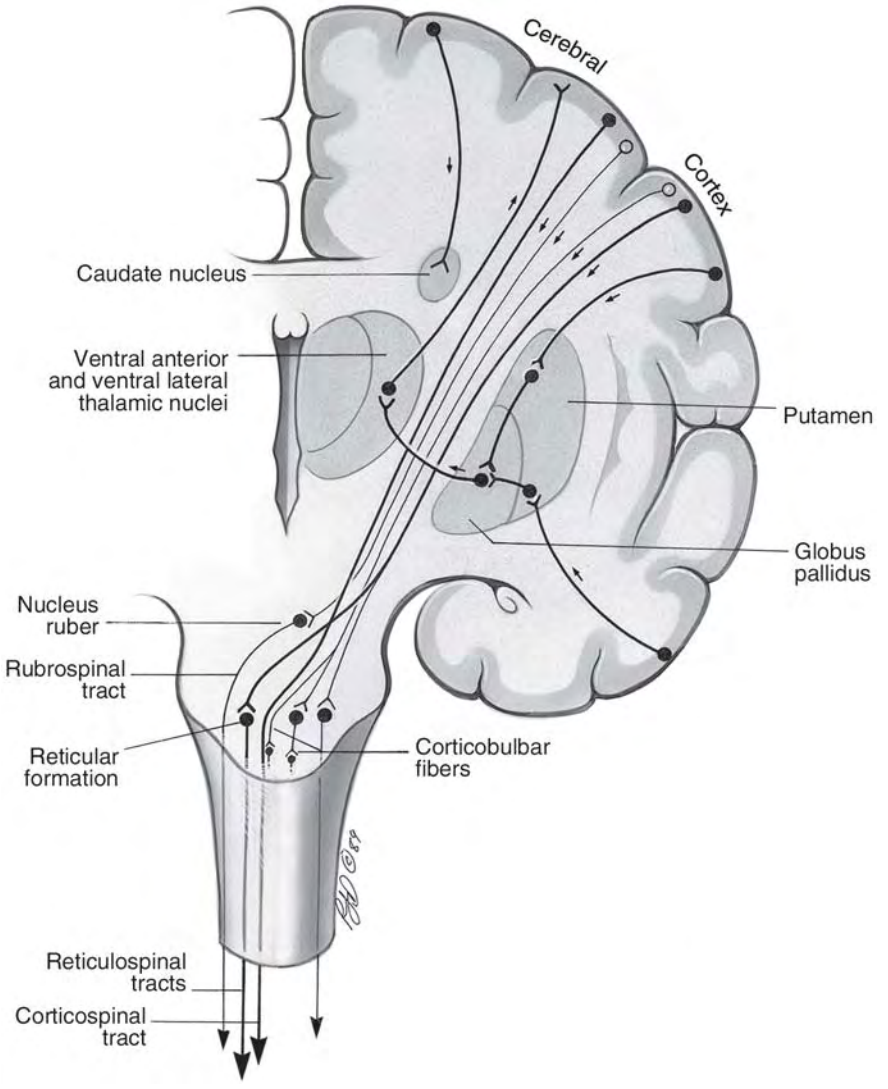
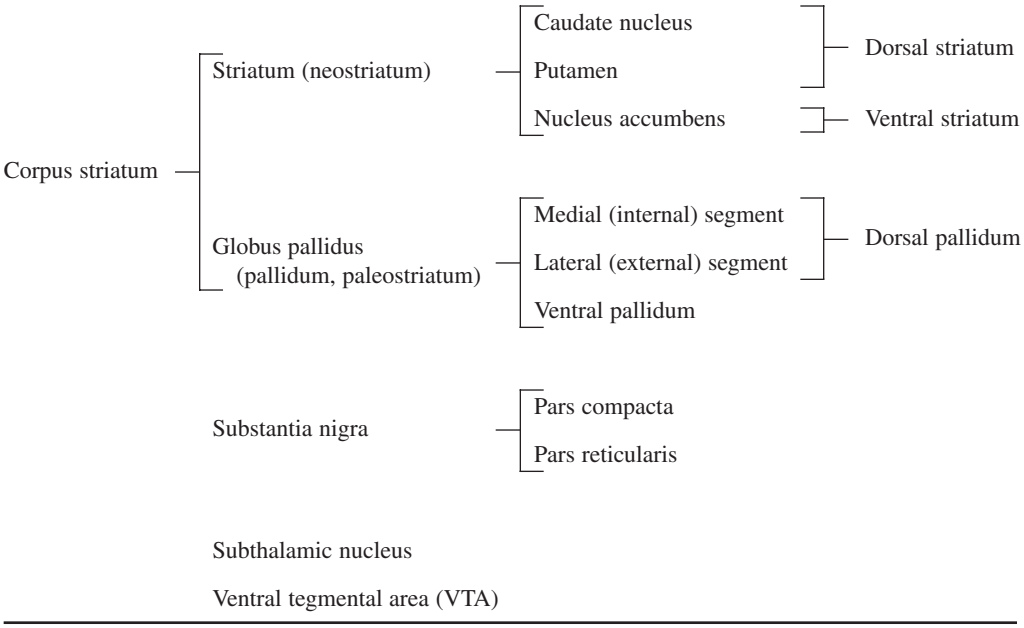


Figure 24.1: The core circuit linking the cerebral cortex, basal ganglia, thalamus, and motor cortex to the descending pathways. The sequence comprises the (1) cerebral cortex to (2) striatum (putamen and caudate nucleus) to (3) globus pallidus to (4) thalamus (ventral anterior and ventral lateral nuclei) to (5) supplementary, premotor, and motor cortices, where (6) the corticospinal, corticorubrospinal, corticoreticulospinal, and corticobulbar pathways originate.

Table 24-1: Basal Ganglia and Related Centers



because of its extensive interrelations with nuclei listed in the table.

The corpus striatum is divided into the striatum (neostriatum) and the globus pallidus (pallidum or paleostriatum). The striatum is divided into the putamen (about 55% by volume), caudate nucleus (about 35% by volume), which together form the dorsal striatum (*see* **Fig. 1.8**), and the nucleus accumbens (ventral striatum). The globus pallidus (GP) is divided into medial (GPm) and lateral (GPl) segments, and ventral pallidum. The substantia nigra consists of two parts, called the pars reticularis and pars compacta based upon differences in neuronal densities. The two parts have different connectivity and neurotransmitters and, hence, are functionally distinct. During development, the fibers of the internal capsule pass through the territory of the basal ganglia and separate (1) the putamen from the caudate nucleus and (2) the subthalamic nucleus and the substantia nigra from the globus pallidus. The putamen and the globus pallidus are collectively called the lenticular (lentiform) nucleus. The (1) caudate nucleus and putamen and the (2) medial segment of the globus pallidus and substantia nigra, pars reticularis (SNr), form two paired units; each pair has similar inputs and outputs (*see* **Fig. 24.2**). The ventral tegmental area (VTA) is a cluster of neurons in the midbrain tegmentum located just medial to the substantia nigra, pars compacta (SNc). The substantia nigra, pars compacta, and VTA both are dopaminergic.

Ventral Striatum and Ventral Pallidum (*see* Table 24.1)

The ventral striatum, which we equate to the *nucleus accumbens although it does encompass some of the adjacent area,* is located ventral to the anterior limb of the internal capsule at the junction of the caudate nucleus and putamen. Its cytoarchitecture and histochemistry are similar to that of the dorsal striatum, which commonly is referred to simply as striatum. The ventral striatum projects to the ventral pallidum. It serves as a link with the limbic system through afferent input from the amygdala and hippocampal formation and output via the ventral pallidum to the dorsomedial thalamic nucleus.

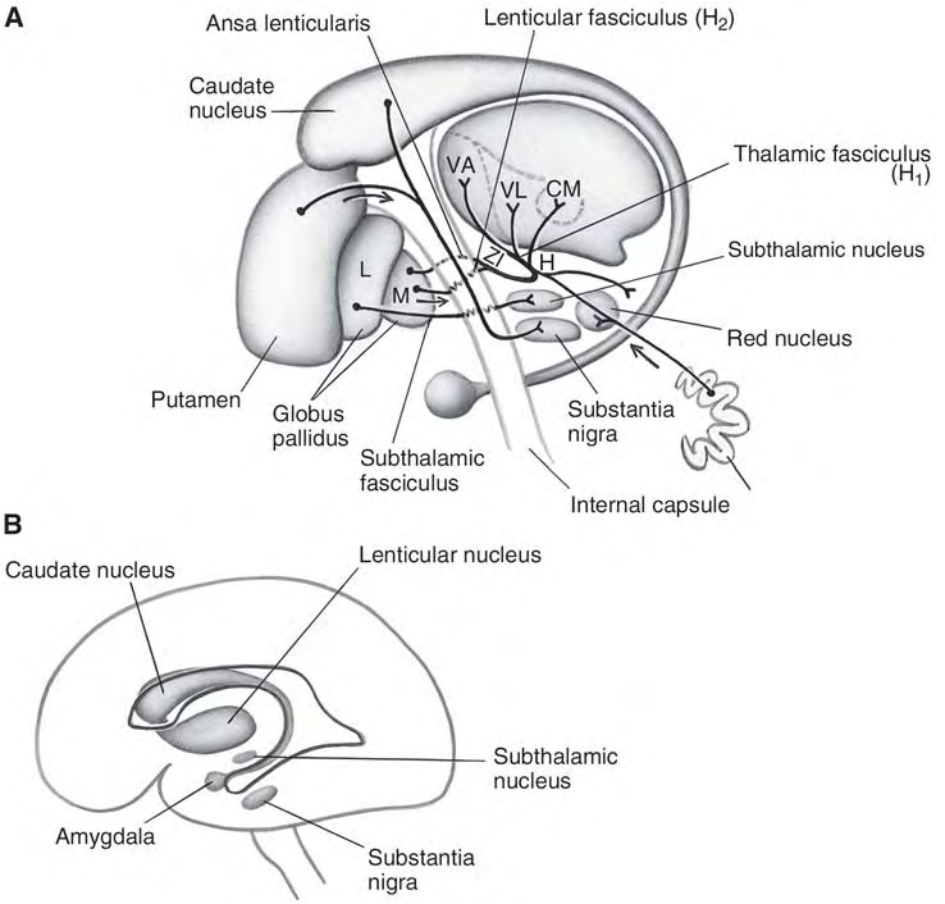


Figure 24.2: Structures involved in the circuitry of the basal ganglia. **(B)** the location of the basal ganglia in relation to the lateral ventricle; **(A)** some efferent projections of the basal ganglia and cerebellum. The pallidofugal fibers from the globus pallidus form three bundles: ansa lenticularis, lenticular fasciculus, and subthalamic fasciculus. The former two bundles and the projections from the dentate nucleus of the cerebellum join to form the thalamic fasciculus that terminates in the thalamus. L and M refer to the medial and lateral segments of the globus pallidus, respectively. VA, ventral anterior thalamic nucleus; VL, ventral lateral thalamic nuclei; CM, centrum medianum; ZI, zona incerta.

The substantia innominata (*see* **Fig. 22.2**) is an area located ventral to and extending rostrally from the basal ganglia. It is associated with the substantia innominata is the basal nucleus of Meynert (Chap. 25) and the ventral pallidum composed of neurons considered to be a ventral extension of the globus pallidus. The *ventral pallidum* has projections that eventually affect descending motor systems. Through these connections, the ventral pallidum together with the ventral striatum are linked to the limbic system and exert a role in

planning and integrating movements that are related to motivational and emotional stimuli.

GENERAL CIRCUITRY ASSOCIATED WITH THE BASAL GANGLIA

The cerebral cortex, basal ganglia, and thalamus are interconnected via several complex neural circuits. Until recently, it was thought that the basal ganglia primarily integrated and processed diverse inputs from wide areas of the neocortex and relayed signals to "motor nuclei" of the thalamus, which projected back to motor regions of the cortex. However, It has become clear that the circuitry of the basal ganglia is in a dynamic state. Components are differentially activated, depending on conditions, and interact as required. Inhibitory and excitatory transmitters, involving numerous comodulators, which act on neurons with a variety of receptor subtypes to produce smooth coordinated movements and behavioral responses, exquisitely modulate activity throughout the system. Pathology of an anatomical or chemical nature can cause profound functional disturbances.

The following representation is abstracted from more complex circuitry. The basal ganglia are composed of a core circuit, which is divisible into at least four functionally segregated parallel circuits (motor, association, oculomotor, limbic), and two side loops, one with the subthalamic nucleus and the other with the substantia nigra.

Generalized Core Circuit

The basic core circuit comprises the cerebral cortex → striatum → globus pallidus → thalamus → cerebral cortex. Processed information then is transmitted via upper motoneuron pathways (e.g., corticospinal tract) to the lower motoneurons. Some structures associated with this circuit are illustrated in **Figs. 24.1–24.4**. A feedback loop goes back to the striatum via thalamostriate fibers from the intralaminar nuclei.

The general core circuit serves as a template for the other parallel cerebral cortex → basal ganglia → thalamocortical loops that convey functionally distinct information from different cortical regions. Each circuit combines a "closed loop" and an "open loop." The "closed loop" comprises the input from a specific cortical area (e.g., supplementary motor cortex) back to the same region (e.g., supplementary motor cortex). The "open loop" component comprises input from other cortical areas (e.g., premotor area, primary motor cortex, and primary somatosensory cortex) and terminates in the cortical area of origin of the closed-loop supplementary motor cortex in the example.

PARALLEL ORGANIZATION OF FUNCTIONALLY SEGREGATED CIRCUITS LINKING BASAL GANGLIA, THALAMUS, AND CORTEX

The basal ganglia–thalamocortical circuits include (1) a motor circuit (*see* **Fig. 24.5A**), (2) an association circuit (*see* **Fig. 24.5B**), (3) an oculomotor circuit (*see* **Fig. 24.5C**), and (4) a limbic circuit (*see* **Fig. 24.5D**). As indicated, the basic design of each circuit incorporates a central "closed loop" and an "open loop," which receives input from several partially overlapping functionally related cortical areas. These multiple inputs are progressively integrated in their passage through the pallidum and thalamus and back to one specific cortical area. None of the loops is a rigid self-contained pathway but, rather, receives diverse influences from the nuclei of the circuit.

The significance of the parallel circuits is that they express another level of organization and functional specificity. Subsidiary inputs and circuits modify and modulate the flow of information that passes through the major basal ganglia–thalamocortical circuits and, thus, provide additional routes for influences to be exerted on these processing centers.

Circuit 1: Motor (*see* Fig. 24.5A)

Widespread areas of the cerebral cortex, including the motor areas, project corticostriate fibers in a topographically organized arrange-

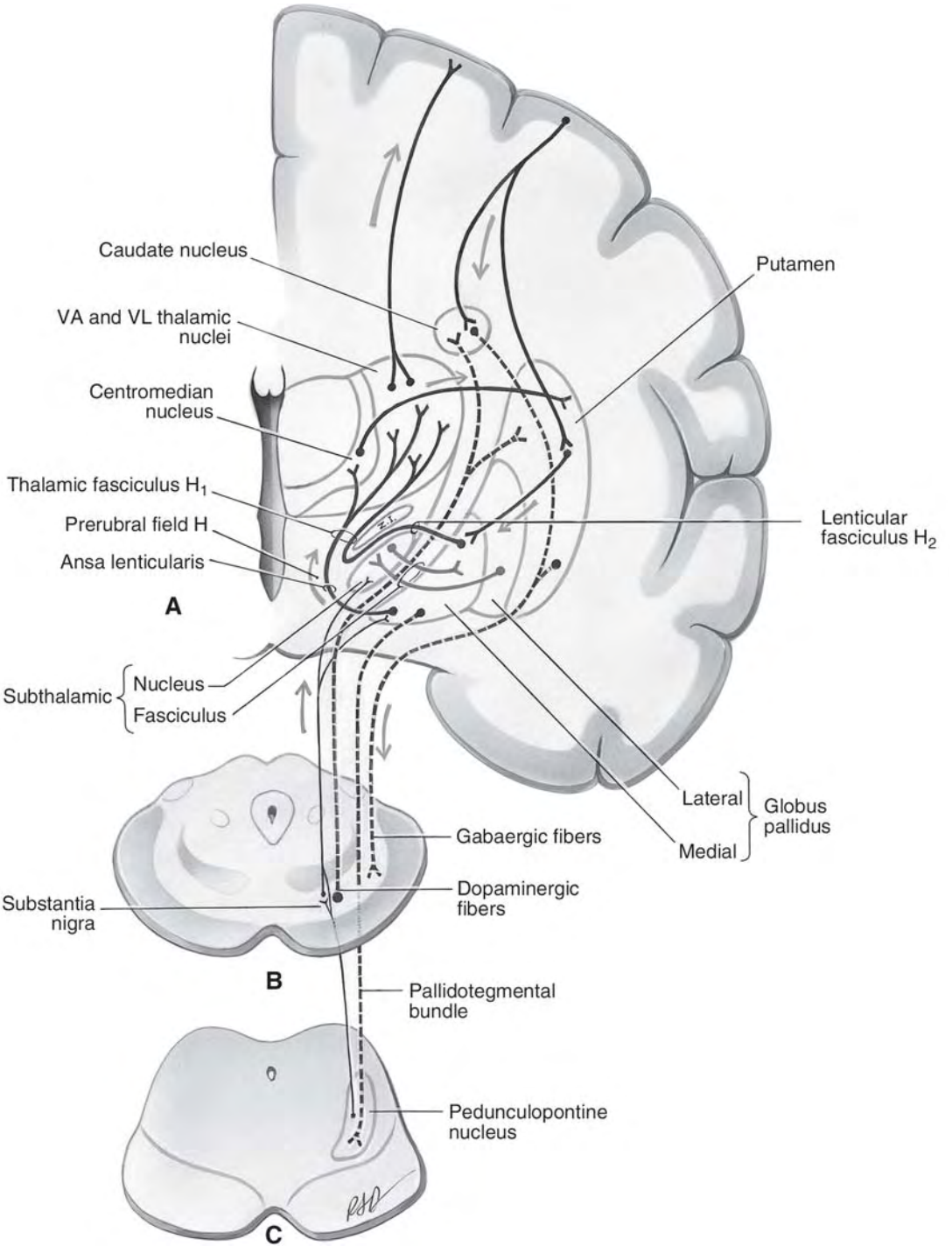


Figure 24.3: Main circuits associated with the basal ganglia are illustrated in **(A)** a coronal section through the cerebrum and **(B,C)** transverse sections through the upper and lower midbrain. *Note:* (1) circuit 1: cerebral cortex to striatum to globus pallidus to VA and VL of thalamus (via

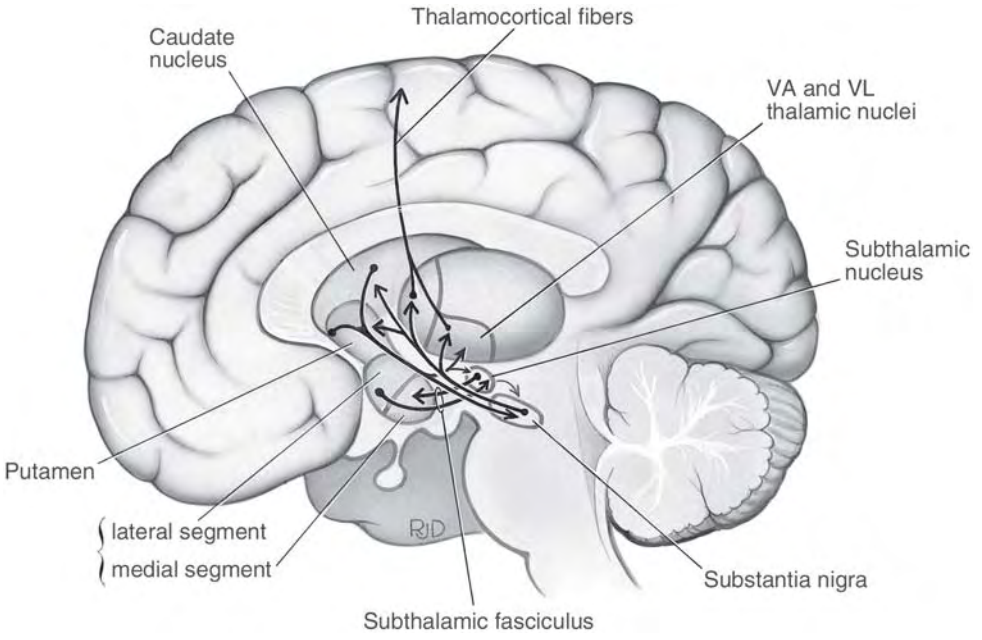


Figure 24.4: Circuits associated with the basal ganglia. *Note:* circuit 2: striatum (caudate nucleus and putamen) to substantia nigra to striatum and to VA and VL thalamic nuclei to motor cortex; circuit 3: globus pallidus to subthalamic nucleus to globus pallidus.

ment to the ipsilateral striatum, particularly the putamen. The motor cortices (areas 4 and 6) and primary somatosensory cortex (areas 3, 1, and 2) project bilaterally to the putamen. The closed-loop portion of the motor circuit begins and ends in the supplementary motor cortex. The open-loop portion involves the other areas.

Striatopallidal fibers arising from all parts of the striatum terminate in both the medial and lateral segments of the globus pallidus. The medial segment is the origin of two fiber bundles, both of which terminate in the thalamus. Fibers from the ventral portion of the globus pallidus form the *ansa lenticularis*, which loops under the internal capsule, whereas fibers from the dorsal portion enter the *lenticular fasciculus*, which passes across the internal capsule and appears as a prominent band as it continues medially along the dorsal and rostral surfaces of the subthalamic nucleus (*see* **Fig. 24.3**). In this location, the lenticular fasciculus forms the ventral border of the zona incerta, which is an extension of the brainstem reticular formation into the diencephalon. Fibers of the lenticular fasciculus and ansa lenticularis coalesce medial to the zona incerta and subthalamic nucleus, where they are just rostral to the red nucleus in what is referred to as the prerubral field. The combined fascicles pass laterally and rostrally along the ventral border of the thalamus (dorsal to the zona incerta) as the *thalamic fasciculus* (*see* **Fig. 24.3**). It should be noted that dentatothalamic fibers from the cerebellum, as well as fibers of the medial lemnis-

ansa lenticularis, lenticular fasciculus, and thalamic fasciculus) to motor cortex; (2) circuit 2: striatum via GABAergic fibers to substantia nigra to striatum via dopaminergic fibers; (3) circuit 3: globus pallidus to subthalamic nucleus and back via subthalamic fasciculus; and (4) circuit 4: striatum to globus pallidus to centrum medianum to striatum. ZI, zona incerta.

cus and spinothalamic tract, also pass through the prerubral field and join the thalamic fasciculus. Pallidal efferent fibers turn dorsally and terminate in the ventral anterior (VA), ventral lateral (VL), and centro median (CM) nuclei of the thalamus. The VA and VL nuclei project somatotopically to lamina IV of the motor cortex (area 4), supplementary motor and premotor cortices, which occupy area 6, frontal eye field (area 8), and prefrontal cortex (areas 9 and 10).

Other connections of this circuit add to the complexity of interactions involving the nuclei of the basal ganglia (*see* **Fig. 24.3**). The globus pallidus, for example, projects to CM and other intralaminar thalamic nuclei; the former, in turn, projects to the putamen as well as diffusely to the cortex. Thus, the intralaminar nuclei are incorporated into a circuit of striatum to globus pallidus to intralaminar nuclei and back. In addition, the globus pallidus has reciprocal connections with the pedunculopontine nucleus of the midbrain (*see* **Fig. 24.3**). The latter does not project caudally. This is consistent with the evidence that none of the basal ganglia has fibers projecting to the lower brainstem or spinal cord. Rather, the output from the basal ganglia is directed toward the cerebral cortex. Several neurotransmitters have been identified with these circuits.

Circuit 2: Association (*see* Fig. 24.5B)

The association circuit is different from the motor and oculomotor circuits in that the widespread association areas of the frontal, parietal, occipital, and temporal lobes project primarily to the ipsilateral caudate nucleus. The closed loop commences and ends in the prefrontal region (areas 9 and 10). Further, striatopallidal connections to the medial segment of the globus pallidus terminate in portions of the nucleus that project preferentially to intralaminar nuclei other than the CM, as well as to the VA and VL. In addition to diffuse cortical collaterals, these other intralaminar nuclei project back to the caudate. Also, the parts of the VA and VL receiving input forward the information to the prefrontal cortex (areas 9 and 10). Other features of this circuit are similar to those of the motor circuit.

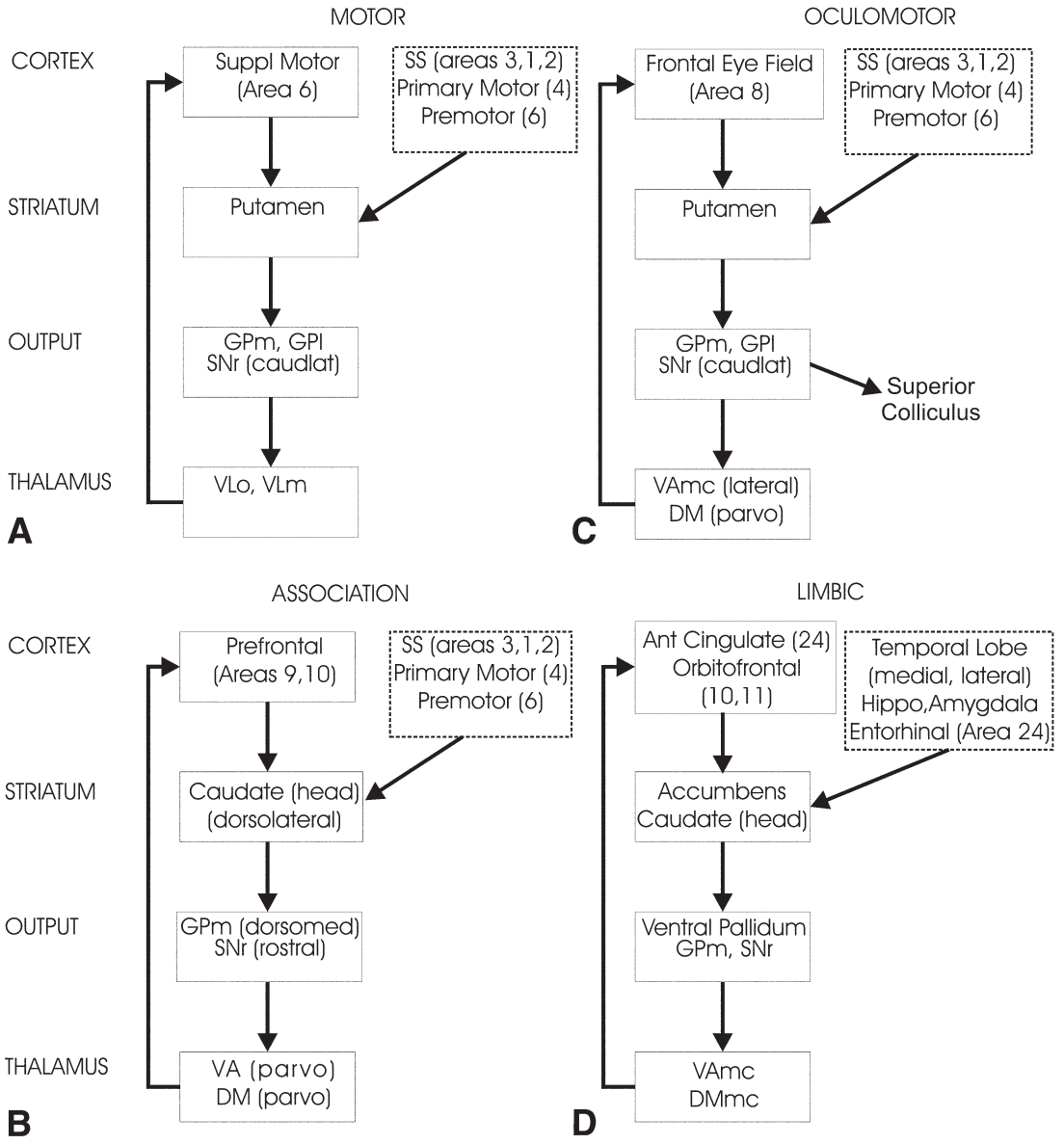
Circuit 3: Oculomotor (*see* Fig. 24.5C)

The closed-loop component of the oculomotor circuit begins and ends in the frontal eye field (area 8). The open loop receives input from the prefrontal cortex (areas 9 and 10) and from the posterior parietal region (area 7). Fibers arising from these cortical areas project preferentially to the body of the caudate nucleus, from which, after processing, information is sent to the globus pallidus and the substantia nigra, the pars reticularis. In addition to projections from these nuclei to the thalamus as in the other circuits (VL, VA, intralaminar), nigral efferents also go to the frontal eye field (area 8) via relays in the dorsomedial nucleus of the thalamus and directly to the superior colliculus to participate in control of saccadic eye movements.

Circuit 4: Limbic (*see* Fig. 24.5D)

There are several separate circuits that can be described as limbic, but they have been combined into one for simplification. The closed-loop portion of a limbic circuit begins and ends in the anterior part of the cingulate

Figure 24.5: Schematic representation of segregated parallel circuits (loops) among the cerebral cortex, basal ganglia, and thalamus. **(A)** Motor loops. The closed loop commences with and terminates in the supplementary motor cortex (area 6). The open loop involves input to the closed loop from somatosensory cortex (areas 3, 1, and 2), primary motor cortex (area 4), and premotor cortex (area 6). **(B)** Association loops. The closed loop commences with and terminates in the prefrontal cortex (areas 9 and 10). The open loop involves input from premotor cortex (area 6) and posterior parietal cortex (area 7). **(C)** Oculomotor loops. The closed loop commences with and terminates in the frontal eye field (area 8). The open loop involves input from the prefrontal cortex (areas 9 and



10) and posterior parietal cortex (area 7). The projection to the superior colliculus has a role in the control of saccadic eye movements. **(D)** Limbic loops. The closed loop commences with the anterior cingulate gyrus (area 24) and orbitofrontal cortex (areas 10 and 11) and terminates in these areas. The open loop involves input from the medial and lateral temporal lobe, hippocampus, amygdala, and entorhinal area (area 24). Ant, anterior; caudlat, caudolateral; DM, dorsomedial thalamic nucleus; mc, magnocellular part; GPl, GPm, globus pallidus, lateral, and medial segments; Hippo, hippocampus; parvo, parvocellular; SNr, substantia nigra, pars reticularis; SS, somatosensory; VA, ventral anterior thalamic nucleus; VL, ventrolateral thalamic nucleus.

gyrus (area 24) and orbitofrontal cortex (areas 10 and 11). The open-loop component receives input from the medial and lateral temporal lobe cortex, including the entorhinal area (area 28), the amygdala, and hippocampus. These regions send excitatory signals (glutamatergic) to the ventral striatum (nucleus accumbens) and part of the head of the caudate nucleus, from which, after processing, information is forwarded to the ventral pallidum, globus pallidus and reticular part of the substantia nigra. Fibers from these nuclei project to the magnocellular divisions of the ventral anterior and dorsomedial thalamic nuclei, which project to the cortex of the closed loop.

SIDE CIRCUITS

Circuit 5: Substantia Nigra

Striatum → substantia nigra → thalamus (VA and VL nuclei) → portions of the motor cortex (*see* **Figs. 24.2 and 24.4**).

This circuit involves the substantia nigra. In brief, the substantia nigra (1) receives input from the ipsilateral striatum, subthalamic nucleus, and globus pallidus and (2) projects to the ipsilateral VL and VA thalamic nuclei (*see* **Fig. 24.5**) as well as back to the striatum (*see* **Fig. 24.2**).

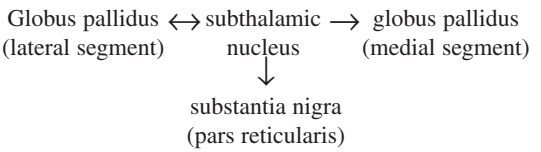
The substantia nigra is divided into the ventrally located pars reticularis, or SNr (adjacent to the crus cerebri) and the dorsally located pars compacta (SNc) (*see* **Fig. 13.15**). The *pars reticularis* has iron-containing glial cells, serotonin, and gamma aminobutyric acid (GABA), but lacks the melanin pigment. The *pars compacta* has dopaminergic neurons that contain melanin (hence, its dark appearance). Neuromelanin pigment is a polymer of the catecholamine precursor dihydrophenylalanine (Dopa) and is absent in patients with Parkinson's disease as well as in infants. There is linkage between the two parts of the nigra via dendrites of pars compacta neurons, which extend into the pars reticularis.

The striatonigral fibers project almost entirely to the pars reticularis, although there are some terminals in ventral parts of the pars compacta. The projections from the substantia nigra are directed rostrally via (1) nigrostriatal fibers from the pars compacta to the striatum and (2) nigrothalamic fibers from the pars reticularis to the VA and VL thalamic nuclei. These thalamic nuclei project to portions of the motor cortical areas. The nigral efferent projections to the VA and VL nuclei terminate in different regions of these thalamic nuclei than do projections from the globus pallidus and from the cerebellum (dentatothalamic fibers); current evidence indicates that no overlap occurs among these three projections.

The substantia nigra, pars reticularis, GPm, and the cerebral cortex are sources of descending fibers to the *pedunculopontine nucleus* (PPN) in the caudal midbrain (*see* **Fig. 24.2**). These fibers are the most caudal projections from the basal ganglia. Other afferents come from the cerebellar nuclei via the superior cerebellar peduncle. Different cells in PPN express acetylcholine and glutamate. Efferents from the pedunculopontine nucleus, which are directed rostrally, mainly go to the substantia nigra, pars compacta, with some to the subthalamic nucleus and to GPm. Thus, PPN is an interface between the cerebellum and the basal ganglia.

The nigrostriatal fibers from the pars compacta form a *dopaminergic system*, which releases dopamine in the striatum. The serotonin in the pars reticularis is derived from the dorsal tegmental nucleus of the midbrain raphe. The striatonigral fibers and the nigrothalamic fibers release GABA.

Circuit 6: Subthalamic Nucleus



(*see* **Figs. 24.2 and 24.4**).

The subthalamic nucleus receives input from the ipsilateral globus pallidus (lateral segment), motor cortex, and pedunculopontine nucleus. It projects output to both seg-

ments of the ipsilateral globus pallidus and to the pars reticularis of the substantia nigra, with which it is reciprocally interconnected; this is another side circuit. The fibers that reciprocally interconnect the globus pallidus and the subthalamic nucleus form the *subthalamic fasciculus*, which passes through the posterior limb of the internal capsule. Neurons of the subthalamic nucleus release glutamate, which is an excitatory transmitter. The subthalamic nucleus is the driving force regulating the output of the globus pallidus and substantia nigra by increasing or decreasing the amount of inhibition they exert on the thalamus (*see* later).

General Organization of the Basal Ganglia

On the basis of their neural connections, the nuclei of the basal ganglia are organized as *input nuclei*, *intrinsic nuclei*, and *output nuclei* (*see* **Table 24.2**). The input nuclei receive afferent information from outside the basal ganglia and project their output to the intrinsic nuclei. The *intrinsic nuclei* interact and have connections with both other input nuclei and output nuclei. After neural processing within the basal ganglia, the *output nuclei* send inhibitory signals to nuclei outside the basal ganglia.

The striatum (caudate nucleus, putamen, and nucleus accumbens) comprises the input nuclei. It receives its major input from the cerebral cortex as well as afferents from the intralaminar nuclei of the thalamus; both pathways are glutamatergic. The globus pallidus (lateral segment), subthalamic nucleus, substantia nigra (pars compacta), and ventral tegmental area comprise the intrinsic nuclei. The circuitry linking these nuclei together and with the input and output nuclei is mainly inhibitory, with GABA as the major neurotransmitter*;* an important exception is the subthalamic nucleus, whose glutamatergic output is entirely *excitatory* (*see* **Fig. 24.6A**). A second rather unusual and very important exception, to be discussed, involves the substantia nigra, pars compacta. The globus pallidus (medial segment), substantia nigra (pars reticularis), and ventral pallidum comprise the output nuclei. The GABAergic projections from these nuclei are largely directed to the thalamus and are *inhibitory* (*see* **Fig. 24.6**).

Cytoarchitectural and Compartmental Organization of the Striatum

Cell Types. The striatum contains two major neuronal population projection neurons whose axons terminate in other nuclei and interneurons whose axons remain within the striatum. *The medium spiny neuron,* which receives most of the extrastriatal input, is, by far, the most numerous cell type, constituting over 90% of the total population. These cells have axons that project out of the striatum; GABA is the major neurotransmitter. Two classes of this cell type, with different projections, are recognized. Striatonigral neurons, including those with collaterals to the medial pallidal segment, corelease substance P and dynorphin; this is referred to as the *direct pathway* to the output nuclei. Striatopallidal neurons to the lateral segment (*indirect pathway*) corelease enkephalin. Both types of spiny neuron have dopamine receptors. There are several different dopamine receptor subtypes; D_1 and D_2 receptors, which activate different intracellular pathways, have been studied most. Recent evidence shows that D_1 and D_2 receptors are colocalized on most spiny neurons, supersed-

Table 24-2:
Categories of Basal Ganglia Nuclei

Input nuclei
Caudate nucleus
Putamen
Nucleus accumbens
Intrinsic nuclei
Globus pallidus (lateral segment)
Subthalamic nucleus
Substantia nigra (pars compacta)
Ventral tegmental area (VTA)
Output nuclei
Globus pallidus (medial segment)
Substantia nigra (pars reticularis)
Ventral pallidum

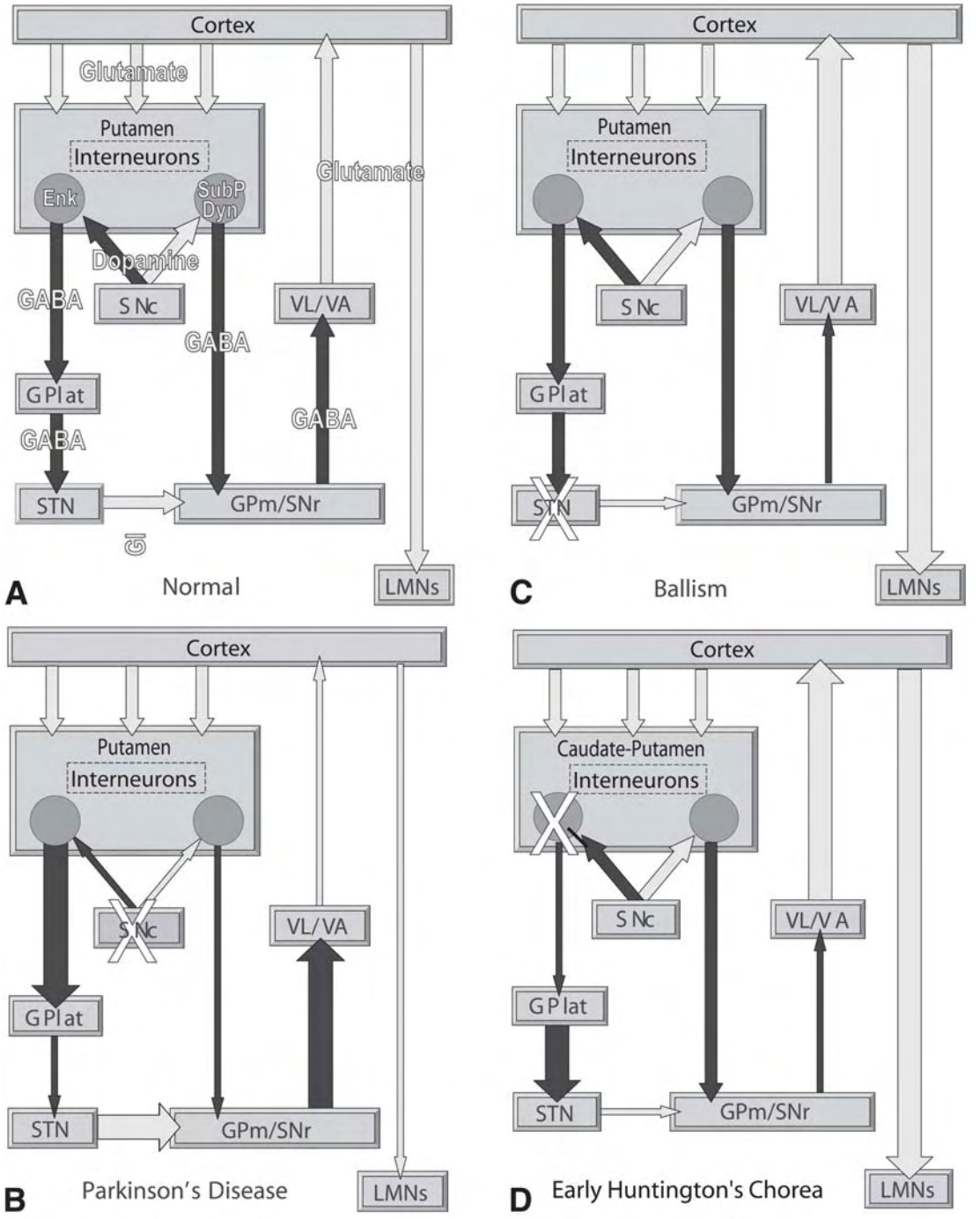


Figure 24.6: Simplified model depicts functional connections of the basal ganglia with the thalamus and cortex whence to lower motoneurons and shows relative balance/imbalance of activity in different parts of the circuitry in normal and various pathological states. Open arrows, excitatory

ing the notion that spiny neurons giving rise to the direct pathway have D_1 receptors, whereas those giving rise to the indirect pathway have D_2 receptors. The two receptor subtypes interact. The dopaminergic input from the substantia nigra presumably differentially modulates the two classes of spiny projection neuron, providing the basis for explaining various forms of basal ganglia-induced motor disturbances (*see* below). Spiny projection neuron axons emit copious collaterals, which inhibit other spiny projection neurons. This is another example of lateral inhibition. In addition, strionigral fibers form presynaptic terminals on the collaterals, adding to the complex modulatory influences on these cells. Collaterals also synapse on interneurons, which terminate on spiny projection neurons and other interneurons. Interneurons, whose axons do not leave the striatum, are of several types. All have dopamine receptors. *Large aspiny neuron* are cholinergic and form excitatory synapses on the projection neurons. In addition, there are two separate classes of intrinsic *medium aspiny neurons* whose major neurotransmitter is GABA. One type also colocalizes somatostatin, nitric oxide, and neuropeptide Y. Thus, different classes of interneurons directly excite or inhibit the projection neurons. Inhibitory interneurons also can indirectly disinhibit them by acting on other inhibitory interneurons, which, in turn synapse upon the projection neurons.

Patch-Matrix Compartments. Based on differences in neurochemical markers, the striatum has been divided into smaller patch compartments (15% of the total) embedded in a matrix. The matrix, in contrast to patches, contains high levels of the enzyme acetylcholinesterase. Only matrix cells contain the calcium-binding protein calbindin D_{28k} and only matrix cells have ϕ opioid receptors. Spiny projection neurons expressing primarily substance P or enkephalin occur in both compartments, but the cortical inputs to the compartments differ. Corticostriate projections from cells in more superficial parts of lamina V go principally to the matrix compartment. Although most of the cortex projects to the matrix, afferents from sensory and motor cortex are differentially distributed to it. Patch compartments receive terminals from neurons in deep parts of lamina V in the cortex related to the limbic system (anterior cingulate and medial frontal gyri), where this lamina is well developed. The two compartments emit distinct striatonigral projections. The matrix sends fibers to the GABAergic parts of SNr, whereas the patches provide input to dopaminergic neurons located in the ventral part of SNc and in islands within SNr.

SUMMARY

The basal ganglia are subcortical nuclei that play a primary role in the integration of somatic motor activity. The amygdala and hippocampus, nuclear complexes of the limbic system (Chap. 22) with connections to the ventral striatum, involve the basal ganglia in somatic

connections; solid arrows, inhibitory connections. Increased excitation or inhibition, thick arrows; diminished effect, thin arrows. **(A)** Normal: all connections are in balance (arrows are the same width throughout). The major neurotransmitters are shown. **(B)** Destruction of the substantia nigra, pars compacta (SNc), as in Parkinson's disease. **(C)** Destruction of the subthalamic nucleus (STN), as in ballism. **(D)** Selective loss of gabaergic striatal projection neurons to the lateral segment of the globus pallidus (GPl), as occurs in early-stage Huntington's chorea. Those projecting directly to the globus pallidus, medial segment (GPm) and to the substantia nigra, pars reticularis (SNr)—the output nuclei of the basal ganglia—also undergo degeneration in later stages. GABA is the major neurotransmitter of spiny striatal projection neurons. Those giving rise to the direct pathway coexpress dynorphin (Dyn) and substance P (Sub P). Those giving rise to the indirect pathway coexpress enkephalin (Enk). LMNs, lower motoneurons; VL/VA, ventral lateral and ventral anterior thalamic nuclei. The striatum contains three types of interneurons. *See* text for description.

movements associated with responses to motivational and emotional stimuli.

The striatum is the receptive complex of the corpus striatum (*see* **Table 24.2**); its input is derived from widespread areas of the neocortex, intralaminar nuclei (centrum medianum and parafascicular nucleus) of the thalamus, substantia nigra, VTA, and dorsal raphe nucleus of the midbrain. The afferent corticostriate influences are mediated by the excitatory transmitter glutamate (*see* **Fig. 24.6A**). The intrinsic local-circuit neurons of the striatum are cholinergic and GABAergic. The striatum is divided into two compartments: 85% consists of a "matrix" and 15% consists of small "patches." The concentration of acetylcholine is much higher in the matrix than in the patches. The matrix receives major input from the motor and sensory cortices. Patches receive major input from the limbic cortex. Two classes of GABAergic medium spiny projection neurons give rise to two separate striatal output pathways: direct and indirect. The direct pathway, which arises from neurons that coexpress substance P and dynorphin, makes monosynaptic connections with the output nuclei of the basal ganglia, the medial segment of the globus pallidus, and the substantia nigra (pars reticularis). The indirect pathway, which arises from neurons that coexpress enkephalin, goes to the lateral segment of the globus pallidus. The GPl sends fibers to the subthalamic nucleus, whose glutamatergic excitatory efferents go to the output nuclei. Striatal projection neurons and interneurons have dopamine receptors. Although there are a variety of subtypes of dopamine receptor, the D_1 and D_2 subtypes, which appear to be colocalized in virtually all projection neurons, have been most thoroughly studied. They are associated with second-messenger systems (Chap. 3). The D_1 receptors act to increase and the D_2 receptors to decrease cAMP formation.

The output of the basal ganglia is derived from neurons of the medial segment of the GP, the substantia nigra (pars reticularis), and ventral pallidum. The projections from these sources to VL and VA thalamic nuclei are distinct and their terminations do not overlap. The thalamic neurons receiving these inputs do not exert major effects on the primary motor cortex (area 4), but, rather, mainly project their outputs to premotor and supplementary motor areas (Chap. 25). The pallidothalamic and nigrothalamic fibers primarily exert inhibitory effects on the thalamus.

The substantia nigra receives input from both the striatum and globus pallidus of the corpus striatum, subthalamic nucleus, pedunculopontine nucleus, and dorsal nucleus of the midbrain raphe. A major output from the substantia nigra (pars compacta) terminates as dopaminergic endings in the striatum. The subthalamic nucleus receives input from the lateral segment of the globus pallidus and the motor cortex and projects to both segments of the globus pallidus, the substantia nigra (pars reticularis), and ventral pallidum. Excitatory influences from the glutamatergic subthalamic nucleus acting on the medial segment of the pallidum and on the substantia nigra (pars reticularis) is regarded as the driving force regulating the output of the basal ganglia.

The basal ganglia along with the cerebellum act as the interface between our sensory systems and many motor responses. The pallidothalamic projections in the thalamus do not overlap the cerebellar projections from the deep cerebellar nuclei. No convergence from the pallidal and cerebellar inputs has been demonstrated on a single thalamic neuron.

The precise role of the basal ganglia in the regulation of normal movements is still a matter of speculation. They are thought to be involved in the regulation of background muscle tone and posture and in the initiation, control, and cessation of automatic movements such as in locomotion (running) and in athletics (throwing a ball). The basal ganglia are apparently involved in the transfer and modification of information from widespread neocortical areas to the motor cortex, especially the premotor and supplementary motor areas. Via circuitry linking the ventral striatum with the limbic system, the basal ganglia participate in behavioral responses related to the emotions.

FUNCTIONAL CONSIDERATIONS

Formerly, the cerebral cortex, especially the motor cortex, was hierarchically placed at the highest level for orchestrating motor integration, and subcortical structures were placed at another level and thought to function solely in a feedback capacity. The newer view states that both the basal ganglia and the cerebellum are crucial in the initial and early processing stages resulting in motor activity. The circuitry involving the sensory cortical areas, basal ganglia, and cerebellum act through the ventral anterior and ventral lateral nuclei, known as the *motor nuclei of the thalamus*. They serve as the main gateway through which these circuits become involved in generating activity in the motor cortical areas; they fire well in advance of and during each volitional movement. In addition, these circuits act as bridges between the sensory cortical areas and the motor cortical areas. In a real sense, these circuits are active participants during all phases of a movement, from initiation to completion.

As we have seen, the role of the basal ganglia, cerebellum, and associated nuclei is to modulate motor activities through circuits, which directly and indirectly feed back to the cerebral cortex. In turn, the cortex projects its influences to the brainstem and spinal levels through the descending motor pathways, upon the local circuitry that activates the alpha and gamma motor neurons. The malfunction of various nuclear complexes results in an imbalance in the interactions within the circuitry of the basal ganglia, disrupting the output, which ultimately is manifest at the level of the motor units. This is a plausible explanation for the variety and assortment of symptoms and signs noted in the disorders involving control of posture and movements. In some disorders, there is an increase in muscle tone to a similar degree in the agonists and antagonists of a muscle group without an accompanying increase in reflex activity, called *rigidity*. Rigidity (Chap. 8) is a form of hypertonus in which the muscles are continuously or intermittently tense, and it is associated with hyperactive static fusiform gamma motoneurons. In contrast, spasticity (Chap. 12) is a form of hypertonus in which the muscles are in phasic hyperactive activity when the muscles are stretched. This is associated with hyperactive dynamic fusiform gamma motoneurons.

Clinical Manifestations

The abnormal involuntary movements called *dyskinesias* can be rhythmic or arrhythmic, generally without paralysis of the muscles. They can be classified as hypokinetic or hyperkinetic. The motor disorders result from improper functioning of the basal ganglia, and associated nuclei, including, among others, paralysis agitans (Parkinson's disease), athetosis, choreas, and ballism.

Paralysis agitans (Parkinson's disease, parkinsonism), which has a mean onset at age 60, is characterized by rigidity and tremor. The rigidity is essentially the same in all muscles; it is accompanied by poverty of movements and *cogwheel rigidity*. Cogwheel rigidity is expressed when the examiner flexes and extends a limb joint of the patient; during movement, an increased resistance suddenly gives way, and as the movement continues, this sequence is repeated, as in a cogwheel. From a standing position, a patient has difficulty taking initial steps. The subject also has the same problem arresting a movement. During forward locomotion, short, shuffling steps are taken. The "masked" face has a fixed expression, accompanied by no overt spontaneous emotional response. The tremor, with a regular frequency (three to six per second) and amplitude, occurs while the subject is at rest; it is lost or reduced during voluntary movement. Degenerative changes in the nigrostriatal pathway, raphe nuclei, locus ceruleus, and motor nucleus of the vagus nerve are present in parkinsonian patients; in addition, there is a marked reduction to absence of dopamine, serotonin, and norepinephrine. It has been shown that Parkinson-like symptoms can be elicited by toxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), that selectively destroy

nigrostriatal dopamine neurons. Administration of L-dihydroxyphenylalanine (L-dopa) in low doses can ameliorate the rigidity, and in high doses, it can ameliorate the tremors. L-Dopa is a precursor of melanin and dopamine.

Although the placement of small lesions in the globus pallidus and VA nucleus of the thalamus in some patients alleviates the symptoms of rigidity and tremor, slowness in the initiation and execution of movement (bradykinesis) does not change. Moreover, the tremor and rigidity often recur a few years after surgery. Modern therapy for parkinsonism includes administration of can -dopa, certain anticholinergics, and/or other agents. Another therapeutic approach being explored is the transplantation of fetal midbrain tissue, including the substantia nigra into the striatum. In primate models of Parkinson's disease, caused by injecting MPTP, subsequent lesions produced in the subthalamic nucleus have been shown to reverse the signs. This is attributed to re-establishment of the appropriate balance of activity within the circuitry of the basal ganglia. A newer treatment option involves deep brain stimulation, in which high-frequency electrical currents are delivered via electrodes implanted bilaterally in the subthalamic nucleus. This produces overexcitation of the globus pallidus, causing it to increase its inhibition of the thalamus and reduce activity in the thalamocortical and descending corticofugal pathways to the lower motoneurons. Clinical trials also have been initiated using gene therapy. One strategy is to transfer glutamic acid decarboxylase, which catalyzes synthesis of GABA, into neurons of the subthalamic nucleus that normally produce glutamate. Increased excitation of the output nuclei is regarded as one aspect causing Parkinson's disease.

Tardive dyskinesia is a form of dyskinesia that occurs in some patients following the chronic administration of phenothiazines (antipsychotic and tranquilizing drugs) as therapy for such psychoses as schizophrenia. The symptoms can include facial grimacing, lip smacking, and choreoathetotic movements of the limbs and trunk. Treatment is to stop giving the drug. Suggested causes include alteration of the dopaminergic receptors, resulting in their hypersensitivity to dopamine. The consequential alteration in the balance among the dopaminergic, intrastriatal, cholinergic, and GABAergic agents results in the involuntary movements.

Choreas (dances) are characterized by jerky, irregular, brisk, graceful movements of the limbs accompanied by involuntary grimacing and twitching of the face. Primarily, the distal segments of the extremities express these movements. In advanced cases, the patient is almost always in motion when awake. There is no reduction in muscle power. *Huntington's disease (chorea)* is a hereditary autosomal dominant disorder (chromosome 4). From its initial subtle symptoms that might not appear until the late thirties, the affliction features progressive increases in the severity of chorea (choreiform movements) and dementia. Death generally occurs 15–20 years after onset. The early stages of the disease have been correlated with a preferential loss, mainly in the caudate nucleus, of the neurons that express enkephalin that project to the lateral segment of the globus pallidus, with a relative sparing of those that project to the substantia nigra and to the medial pallidal segment. The latter are affected in later stages. Although not markedly degenerated, the cholinergic interneurons clearly are damaged in later stages, as evidenced by a significant reduction in the amount of striatal cholinesterase. A reduction in substance P and enkephalin in the globus pallidus and substantia nigra also occur. The involuntary choreiform movements are presumed to result from disturbances in metabolism and outputs of the neuronal loops involving the GABAergic spiny projection neurons, dopaminergic nigrostriatal, and cholinergic intrastriatal neurons. The impaired cognitive function is attributed to a concomitant loss of neocortical neurons.

The movements of *athetosis* are slow and exaggerated by voluntary movement. The slow, writhing character of the involuntary movements of the neck, trunk, and extremities

appear wormlike. The alternating adduction and abduction of the shoulder joint is accompanied by flexion and extension of the wrist and fingers. Usually, the wrist is flexed, and the fingers hyperextended. Facial grimaces might occur during the limb movements. This dyskinesia could be the result of a lesion in the striatum, mainly in the putamen. Athetosis is frequently associated with cerebral palsy. It occurs as the result of brain lesions during or prior to birth.

Ballism ("throwing") is characterized by violent, high-amplitude, flaillike movements originating mainly from the activity of the proximal appendicular muscles of the shoulder and pelvis. The movements cease during sleep. There is a reduction of muscle tone. These symptoms are exhibited unilaterally with a lesion in the contralateral subthalamic nucleus. Because, clinically, ballism almost always occurs on one side only and is usually the result of a vascular accident, it is also known as *hemiballism*. Symptoms associated with malfunctioning of the basal ganglia are usually observed bilaterally. However, like hemiballism, lesions on one side are manifest on the opposite side because the output of the basal ganglia is directed toward the ipsilateral cerebral cortex whose descending pathways predominantly innervate lower motoneurons on the contralateral side.

The abnormal movements resulting from lesions in the basal ganglia circuitry are an expression of release phenomena, in which the inhibitory influences on such structures as the globus pallidus or ventral lateral nucleus of the thalamus are lost or reduced. Surgical lesions of these "released structures" (globus pallidus and VL) are known to ameliorate the symptoms in many patients. In this context, the loss of dopamine, noted in patients with parkinsonism, accounts for the reduction or loss of inhibitory influences upon the striatum. A likely underlying cause of disorders of the basal ganglia is that disruptions in transmitter metabolism result in an abnormal output from the circuitry of the basal ganglia.

Alterations of Inhibitory/Excitatory Activity in Movement Disorders

As indicated earlier, motor activity is modulated by the basal ganglia via their inhibitory output to the thalamus and excitatory thalamocortical–upper motoneuronal pathways. Smooth, coordinated "normal" movements require a proper balance of excitatory and inhibitory activity throughout the basal ganglia (*see* **Fig. 24.6**A). Anything that alters the usual pattern of inhibition exerted upon the thalamus is in a position to disrupt normal motor function. Thus, increased inhibition of the thalamus might be expected to diminish excitatory activity of the thalamocortical–upper motoneuronal pathways and reduce or otherwise impoverish motor activity. Conversely, decreased inhibition of the thalamus might be expected to increase excitation of the thalamocortical– upper motoneuronal pathways and produce an excess of motor activity.

Based on the circuitry of the basal ganglia and the interplay of inhibitory and excitatory neurotransmitters, the bradykinesis characteristic of parkinsonism is attributed to increased activity of the basal ganglia output nuclei (medial segment of the globus pallidus; substantia nigra, pars reticularis), which inhibit the VA and VL nuclei of the thalamus (*see* **Fig. 24.6B**). An unusual feature of the circuitry of the basal ganglia is that dopamine in the nigrostriatal pathway presumably inhibits the enkephalin-expressing striatal spiny projection neurons that give rise to the indirect pathway and excites the substance P- and dynorphin-containing neurons that form the direct pathway. Following this scheme, loss of dopaminergic nigrostriatal neurons, an attribute of this disease, causes reduced inhibition selectively of the striatopallidal fibers to the lateral segment of GP). Thus, the GPl receives greater than usual inhibitory input, causing its inhibitory influence on the subthalamic nucleus to be reduced. As a consequence, the excitatory influence of the subthalamic nucleus upon GPm/SNr is increased. These output nuclei inhibit the VL and VA to a greater than customary degree, ultimately reducing the

activity of the lower motoneurons. Diminished excitation of the striatal neurons that project directly to the GPm/SNr simultaneously occurs. This reduces inhibition on the GPm/SNr, leading to increased inhibition of the thalamus, as via the indirect pathway.

Conversely, lesions of the subthalamic nucleus decrease excitation of GPm/SNr, resulting in diminished inhibition of the thalamocortical part of the circuit (*see* **Fig. 24.6C**). Thus, activity of the lower motoneurons is increased above usual levels, as occurs in ballism. Following this line of reasoning, lesions of the subthalamic nucleus, produced in MPTP-induced models of parkinsonism, should restore the balance of activity in the internal circuitry of the basal ganglia. Indeed, this has been demonstrated to occur. With lesions of the substantia nigra, there is excessive activity in the subthalamic nucleus, regarded as an important factor in the generation of Parkinson's disease. In the primate model, this excessive activity is eliminated with the secondary lesion.

As noted, Huntington's chorea in the early stages is associated with lesions of the striatum (mainly caudate) selectively involving the enkephalin-expressing GABAergic projection neurons whose axons terminate in the lateral segment of the pallidum. Reduced inhibition upon the GPl would cause greater inhibition of the subthalamic nucleus (*see* **Fig. 24.6D**). In turn, excitation of GPm/SNr would be reduced, causing less inhibition of VL and VA, as after lesions of the subthalamic nucleus directly. Thus, the end result would be increased activity of the lower motoneurons, expressed as a hyperkinetic movement disorder. However, the pattern as well as amount of activity might be expected to be different from that elicited by other pathologies, accounting for the dissimilarities in movement disorders.

SUGGESTED READINGS

Aizman O, Brismar H, Uhlen P, et al. Anatomical and physiological evidence for D1 and D2 dopamine receptor colocalization in neostriatal neurons. *Nature Neurosci.* 2000;3:226–230.

Bates G, Harper PS, Jones L. *Huntington's Disease.* New York: Oxford University Press; 2002.

Brady AM, O'Donnell P. Dopaminergic modulation of prefrontal cortical input to nucleus accumbens neurons in vivo. *J. Neurosci.* 2004;24:1040–1049.

Gerfen CR. D1 dopamine receptor supersensitivity in the dopamine-depleted striatum animal model of Parkinson's disease. *Neuroscientist* 2003;9:455–462.

Guzman JN, Hernandez A, Galarraga E, et al. Dopaminergic modulation of axon collaterals interconnecting spiny neurons of the rat striatum. *J. Neurosci.* 2003;23:8931–8940.

Haber SN, Fudge JL, McFarland NR. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J. Neurosci.* 2000;20:2369–2382.

Kawaguchi Y. Neostriatal cell subtypes and their functional roles. *Neurosci. Res.* 1997;27:1–8.

Kelly RM, Strick PL. Macro-architecture of basal ganglia loops with the cerebral cortex: use of rabies virus to reveal multisynaptic circuits. *Prog. Brain Res.* 2004;143:449–459.

Luo J, Kaplitt MG, Fitzsimons HL, et al. Subthalamic GAD gene therapy in a Parkinson's disease rat model. *Science* 2002;298:425–429.

Matsumura M, Kojima J. The role of the pedunculopontine tegmental nucleus in experimental parkinsonism in primates. *Stereotact. Funct. Neurosurg.* 2001;77:108–115.

Obeso JA. *The Basal Ganglia and New Surgical Approaches for Parkinson's Disease.* Philadelphia, PA: Lippincott-Raven; 1997.

Obeso JA, Rodriguez-Oroz MC, Rodriguez M, Arbizu J, Gimenez-Amaya JM. The basal ganglia and disorders of movement: pathophysiological mechanisms. *News Physiol. Sci.* 2002;17:51–55.

Onn SP, West AR, Grace AA. Dopamine-mediated regulation of striatal neuronal and network interactions. *Trends Neurosci.* 2000;23:S48–S56.

Parent A, Levesque M, Parent M. A re-evaluation of the current model of the basal ganglia. *Parkinsonism Relat Disord.* 2001;7:193–198.

Plenz D. When inhibition goes incognito: feedback interaction between spiny projection neurons in striatal function. *Trends Neurosci.* 2003;26: 436–443.

Reynolds JN, Wickens JR. Dopamine-dependent plasticity of corticostriatal synapses. *Neural Netw.* 2002;15:507–521.

Rodriguez-Oroz MC, Rodriguez M, Guridi J, et al. The subthalamic nucleus in Parkinson's disease: somatotopic organization and physiological characteristics. *Brain* 2001;124:1777–1790.

Steiner H, Gerfen CR. Role of dynorphin and enkephalin in the regulation of striatal output pathways and behavior. *Exp. Brain Res.* 1998;123:60–76.

Tunstall MJ, Oorschot DE, Kean A, Wickens JR. Inhibitory interactions between spiny projection neurons in the rat striatum. *J. Neurophysiol.* 2002;88:1263–1269.

West AR, Floresco SB, Charara A, Rosenkranz JA, Grace AA. Electrophysiological interactions between striatal glutamatergic and dopaminergic systems. *Ann. NY Acad. Sci.* 2003;1003: 53–74.

Wichmann T, DeLong MR. Functional neuroanatomy of the basal ganglia in Parkinson's disease. *Adv. Neurol.* 2003;91:9–18.

Wise SP, Murray EA, Gerfen CR. The frontal cortex–basal ganglia system in primates. *Crit. Rev. Neurobiol.* 1996;10:317–356.

25
Cerebral Cortex

Organization of the Neocortex
Motor Areas of the Neocortex
Sensory Areas of the Neocortex
Higher Cortical Association Areas
Blood Flow in the Cortex
Split-Brain Man and Cerebral Dominance
Memory

The highest of human functions involve the intricate circuitry of the cerebral cortex, which has crucial roles in language, conceptual thinking, creativity, planning, and the ways in which we give form and substance to our thoughts. Our abilities in this realm are the result of the enlargement of the neocortex, particularly of the association cortex, one of the most striking features of mammalian evolution. The cortex enables us to appreciate the fine qualities of sensation and to organize skilled motor activities. Our multifaceted patterns of response require a continuous stream of sensory input and interactions of the cortex with the thalamus and subcortical nuclei such as the basal ganglia. Conscious awareness of self, both internal and in relation to the environment, is cortical expressions.

The cerebral cortex is the 600-g gray covering of the cerebrum, constituting about 40% of the brain by weight and containing 100 billion or more neurons. Of the total mass, the neurons weigh about 180 g and the glial cells and blood vessels weigh about 420 g.

The cerebral cortex is divided into the phylogenetically older *allocortex*, about 10% of the total, and in mammals, the more recently evolved six layered *neocortex* (*isocortex*), about 90% of the cortex in humans. The *allocortex, which does not receive thalamic input,* consists of the ancient three-layered *archicortex,* which is limited to the hippocampal formation (hippocampus and dentate gyrus), and the *paleocortex,* composed of the six-layered parahippocampal gyrus, and the olfactory cortex or uncus. A form of the neocortex that might have features not as advanced as the bulk of this type is sometimes referred to as the *mesocortex;* it includes the cingulate gyrus, fasciolar gyrus, and the isthmus (*see* **Fig. 1.7**). The allocortex and mesocortex incorporates the *limbic lobe* (Chap. 1), an artificial construct formed from parts of other lobes, located on the medial aspect of the hemisphere, where it forms a ring around the corpus callosum and rostral brainstem. The neocortex consists of the cortex of the frontal, parietal, occipital, temporal, and central lobes, excluding the allocortex (Chap. 1).

The neocortex has been parceled in several ways; the most commonly used scheme is that of Brodmann (1909), who numbered areas consecutively, based on cytoarchitectural differences visualized in Nissl-stained preparations. More than 40 areas, out of a total of 52, are discernable on the lateral and medial surfaces of the brain (*see* **Figs. 25.5 and 25.6**). Nonadjacent areas frequently express the same features. Later, von Economo (1920) categorized the neocortex into a continuum of five different cytoarchitectural types. The two extremes are referred to as *heterotypic* and include the primary sensory cortices and motor cortex. The former is the thinnest cortex (about 2 mm from pial surface to white matter), and because of a

large population of small stellate-shaped perikarya in a particularly well-developed layer IV that resemble sand, it is called *hypergranular*. The heterotypic motor cortex is more than twice as thick and is called *agranular* because of the lack of a well-defined layer IV. In addition, layer IV of this region is characterized by the presence of small pyramidal cells, and layer V is enlarged. The great majority of cortex, comprising the association areas, is referred to as *homotypic* and includes the middle three gradations. The six layers are more readily differentiated in this type of cortex.

ORGANIZATION OF THE NEOCORTEX

The neocortex is conventionally described as being organized in six horizontal laminae oriented parallel to the cortical surface (*see* **Fig. 25.1**). Individual laminae are somewhat obscured in the heterotypic cortex, where some laminae are highly developed and others are attenuated. In some areas, different laminae are subdivided. Although lamination is its most conspicuous feature, the basic functional units of the cerebral cortex are physiologically defined vertical columns or modules extending from the pial surface to the white matter (*see* **Fig. 25.2**). These are not columns in the architectural sense, but, rather, are long three-dimensional slabs up to 0.5 mm in width. Most cortical columns are (1) the terminus of afferent fibers from other cortical areas and the thalamus and (2) the source of efferent fibers terminating in other cortical columns of the same hemisphere (*association fibers*), in the same cortical area of the contralateral hemisphere (*commissural fibers passing through the corpus callosum or anterior commissure*), and in subcortical nuclei of the cerebrum, brainstem, and spinal cord (*projection fibers*). In general, the main input layers of the cortex are laminae I through IV. The main output is from laminae V and VI. However, both association and commissural fibers take origin from laminae II and III and terminate in the same laminae elsewhere in cortex. The input to the neocortex, aside from association and commissural fibers, is derived primarily but not entirely from the thalamus. The output from the neocortex to subcortical regions is relayed via projection fibers—corticobulbar, corticoreticular, corticopontine, corticothalamic, corticostriate, corticorubral, corticonuclear, and corticospinal.

Neurons of the Neocortex (*see* Figs. 25.1 and 25.2)

Five basic neuronal cell types (pyramidal, stellate, stellate [star] pyramidal, Martinotti, horizontal) are representative of the numerous cortical neurons. The shape of the cell body, dendritic organization, and course taken by its axon are among the criteria used to characterize a cell. Pyramidal cells, present in all but the first layer, constitute the majority of cortical neurons. Each *pyramidal cell* has a cell body shaped like an isosceles triangle with a single branched *apical dendrite* extending toward the cortical surface and several horizontally directed branched *basilar dendrites.* The *axon* typically arises from the base and, except for some in layer II, enters the subcortical white matter; usually, there is a collateral branch (*recurrent collateral*) going back toward the pial surface. The main axonal branches of the pyramidal cells form the association fibers, commissural fibers, and projection fibers listed above. Pyramidal cells, depending on the size of the soma, are described as small, medium, large, or giant. The latter, called *Betz cells*, are about 100 μm high and are restricted to cortical lamina V of area 4 (Chap. 11). The designations external (III) and internal (V) pyramidal layers are derived from the neurons that characterize them. Although layer II is called the external granular layer, it is actually largely populated by *small pyramidal neurons*. *Stellate cells* are multipolar interneurons with a star-shaped body, short-branched dendrites, and a short axon that arborizes and synapses with other cortical neurons in the immediate vicinity. Stellate cells, which are local circuit (Golgi type II) neurons, comprise two distinct morphological and functional populations, namely

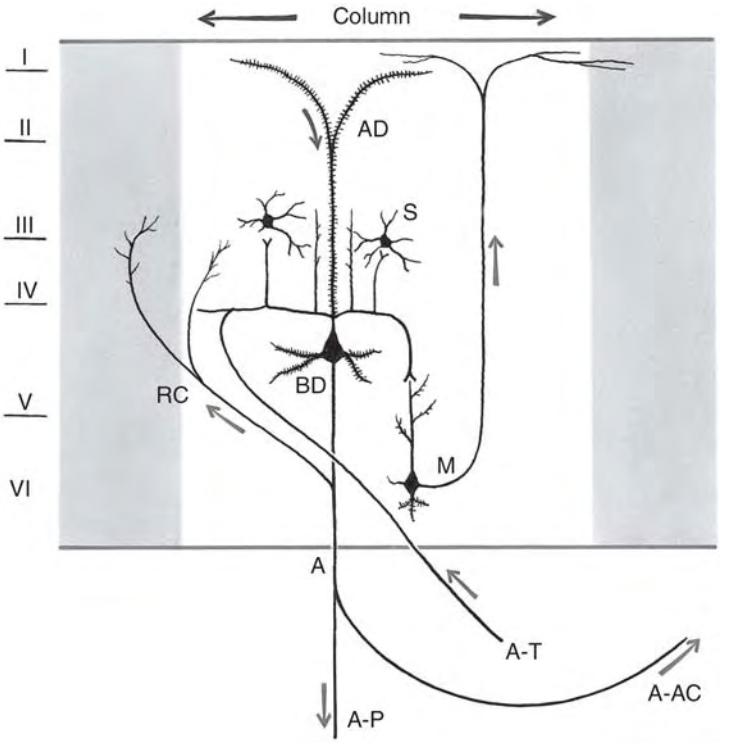


Figure 25.1: Vertical columnar organization of the neocortex. Roman numerals indicate the six horizontal laminae. The cell bodies of the pyramidal neurons and stellate (granule) neurons are present in laminae II through VI. Each pyramidal neuron is oriented in a vertical plane, with its apical dendrite extending to lamina I and its basilar dendrites extending horizontally. Its axon extends out of the cortex into the white matter and has recurrent branches projecting back to the cortex. The dendrites and axon of each stellate neuron (S) arborize and terminate within the immediate column. The axon of each Martinotti neuron (M) has an axon that extends from lamina VI to laminae II and I. A, axon of a pyramidal neuron; A-AC, axon of an association or commissural neuron; AD, apical dendrite of pyramidal neuron; A-P, axon of projection neuron; A-T, corticopetal axon from a neuron of a specific relay or association nucleus in the thalamus; BD, basilar dendrites of a pyramidal neuron; RC, recurrent collateral.

excitatory neurons and inhibitory ones. The latter, referred to as *aspiny neurons* because of a lack of dendritic spines, are mainly GABAergic (GABA is the major inhibitory neurotransmitter). *Spiny stellate cells* are glutamatergic. Glutamate is regarded as the major excitatory neurotransmitter of the cerebral cortex. Many cortical neurons have comodulators. Stellate cells are particularly conspicuous in lamina IV, and because of their appearance in the Nissl stain, this lamina is called the internal granular layer. Stellate cells exhibit a variety of shapes and sometimes are referred to with names such as *double bouquet cells, tuft cells, chandelier cells,* and *basket cells* (*see* **Fig. 25.2**). Except for the double bouquet cells, they are all regarded as aspiny inhibitory interneurons. *Stellate pyramidal neurons* are large cells that combine the features of both stellate and pyramidal cells. These neurons have a stellate shape with an apical dendrite together with numerous dendrites radiating from the cell body. Stellate pyramidal neurons are characteristic of lamina VI and have an axon that enters

the subcortical white matter. *Martinotti cells* are multipolar interneurons with short-branched dendrites and a branching axon that ascends toward the cortical surface, forming synapses with other cortical neurons. The *horizontal cell (of Cajal)* is a small neuron of the most superficial cortical lamina that is absent or rare in adults; its axon is oriented parallel to the cortical surface. Lamina I is referred to as the molecular layer because it mainly consists of neuronal processes and contains relatively few cell bodies. Except for the pyramidal and the stellate pyramidal cells, all cortical cells are intracortical interneurons.

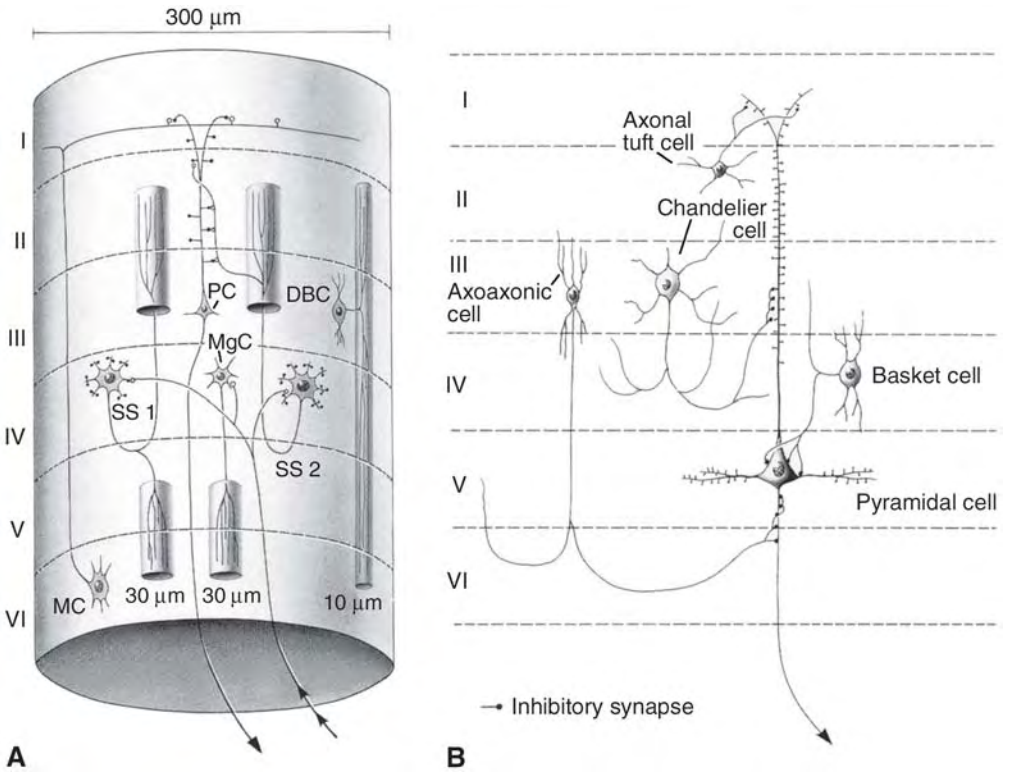


Figure 25.2: (A) Modular organization of the neocortex as formed by the afferent inputs from specific thalamic nuclei, commissural and association fibers. Note (1) the vertical cylindrical distribution of the axons of the intrinsic neocortical interneurons and (2) that all neurons and fibers illustrated have putative excitatory synaptic connections with the pyramidal neurons. **(B)** Cortical interneurons that have putative inhibitory synaptic connections that inhibit the pyramidal neurons; the cells illustrated are varieties of aspiny Golgi type II neurons. Different interneurons inhibit various segments of the pyramidal neurons; the inhibitory axoaxonic synapses of the axoaxonic cells just distal to the axon hillock of the pyramidal cell can act as the final processing mechanism regulating the discharge of the pyramidal neuron (Dendrite–Cell Body Unit, Chap. 3). The processing also includes the disinhibition of interneurons by inhibitory synapses from other interneurons (not illustrated). Fibers from the pyramidal neurons of (1) lamina VI project to the thalamus, (2) those of lamina V project to thalamic association nuclei and other subcortical structures (e.g., striatum, brainstem, and spinal cord), and (3) those of laminae II and III project to other areas of the cerebral cortex. DBC, double bouquet cell; MgC, microgliaform cell; MC, Martinotti cell; PC, pyramidal cell; SS, stellate cell. (Adapted from Szentagothai, 1978.

The input to the columns of the neocortex is derived primarily from other cortical areas (largest), thalamus, substantia innominata, locus ceruleus, brainstem raphe nuclei, and basal nucleus of Meynert; there are other sources of corticopetal fibers. In general, fibers from the thalamic relay nuclei terminate in a rich arborization within lamina IV, fibers from nonspecific nuclei terminate mainly in layers I, V, and VI, and afferents from other cortical areas terminate primarily in layers II and III. The axon collaterals of the pyramidal cells and the axons of many interneurons are oriented vertically. The lateral spread of the axons and dendrites is minimal. These neurons are interconnected into numerous chains of small and long loops. The locus ceruleus and, possibly, the raphe nuclei are excited by novel stimuli in the environment; each adrenergic fiber from the locus ceruleus arborizes widely in the output cortical laminae V and VI, whereas each serotonergic fiber from the raphe nuclei arborizes widely in the input cortical laminae I to IV. The result is that the diffuse projections from these nuclei have global effects upon both the limbic system and cerebral cortex (*see* Prefrontal Cortex).

Functional Aspects

The cerebral cortex has been subdivided into areas described in terms of several structural and functional criteria. The functions of the cortex are inferred from subjective accounts and objectively observed responses of subjects (1) who have had areas of cortex damaged by lesions or surgical ablation, (2) in whom cortical sites were stimulated electrically, and (3) who have irritative lesions resulting in epileptic seizures. Evidence based on ablation generally reveals how the nervous system functions without the ablated part, but does not necessarily reveal more than the general role of the part. An enormous amount of information concerning the function of different areas of the cortex has been generated in recent years using imaging techniques such as positron-emission tomography (PET) and functional magnetic resonance imaging (MRI).

Functionally defined areas of the neocortex comprise the (1) sensory areas, including primary sensory areas, secondary sensory areas and association areas, (2) motor areas, including primary motor area, premotor areas, and supplementary motor area, and (3) "psychical" and prefrontal areas.

MOTOR AREAS OF THE NEOCORTEX

Primary Motor Cortex

The primary motor cortex is located in area 4 of the precentral gyrus (*see* **Fig. 25.3**). Direct electric stimulation of this region evokes movements of the voluntary muscles on the opposite side. A map of this electrically excitable motor cortex produces a motor homunculus. **Figure 25.4** depicts both the motor and sensory homunculi. The homunculus is upside down, with the head region near the lateral fissure and the lower extremity on the medial surface in the paracentral lobule. The amount of motor cortex devoted to specific body regions is roughly proportional to the delicacy of control and innervation density of that region (e.g., large areas for fingers, thumb, lips, and tongue). Ablation of this cortex results in marked contralateral paresis, flaccidity, hyperactive deep tendon reflexes, and positive Babinski reflex and is followed by moderate motor recovery. (Note similarities to and differences from upper-motoneuron paralysis; Chap. 12.)

Premotor Cortex and Supplementary Motor Area (*see* Figs. 25.3 and 25.4)

The premotor cortex consists of areas 6 and 8. The supplementary motor area is in area 6 on the medial aspect of the frontal lobe. Stimulation of this supplemental area elicits responses that are largely bilateral synergistic movements of a tonic or postural nature, affecting primarily the axial muscles and proximal muscles of the extremities. The responsive area outlines a small homunculus with its head located rostrally. Stimulation of area 6 on the lateral cerebral surface produces aversive movements;

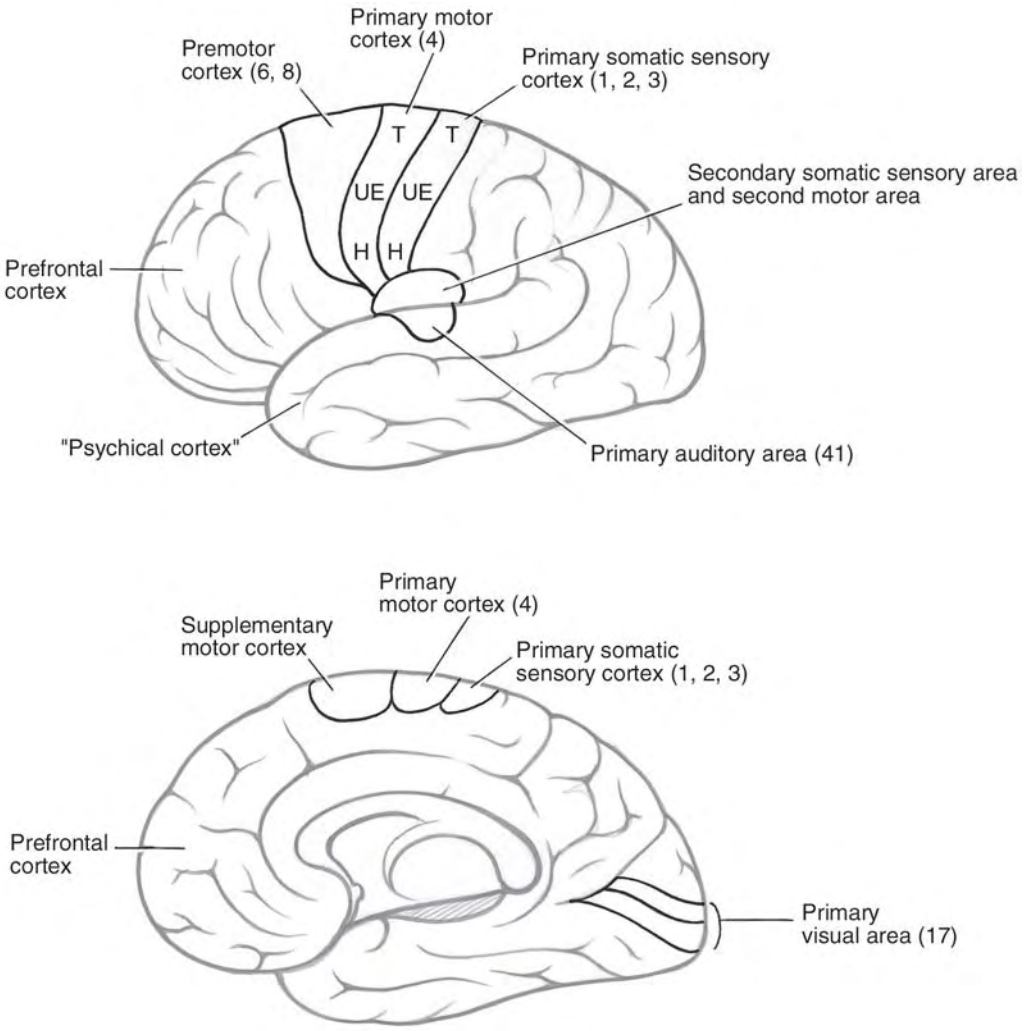


Figure 25.3: The location of several functional areas of the cerebral cortex. The representation of body parts of the primary motor and somatic sensory (somatosensory) cortices includes the head (H), upper extremity (UE), trunk (T), and lower extremity (LE). Numbers represent areas of Brodmann.

these "orientation" movements are generalized actions, such as turning of the head and eyes, twisting movements of the trunk, and general flexion or extension of the limbs. Bilateral ablation of the supplementary motor area in the monkey results in hypertonus of flexor muscles and increased resistance to passive movements in the limbs, but it does not cause paresis.

Note that the symptoms of an upper-motoneuron (UMN) paralysis can be produced by lesions of both the primary motor cortex and supplementary cortex, but not of either separately. This suggests that the symptoms of UMN paralysis are probably the result of interruption of fibers from the primary motor cortex, supplementary motor cortex, and premotor cortex as they pass through the internal capsule.

The *primary motor cortex* participates in the initiation of skilled, delicate, and agile volun-

tary movements. Although the primary motor cortex has a critical role in the control of the distal limb muscles on the contralateral side of the body, it also contributes to the regulation of axial and proximal limb musculature. The *premotor cortex* on the lateral surface of the frontal lobe has (1) a primary role in the control of proximal limb and axial musculature and (2) an essential role in the initial phases of orientation movements of the body and upper limb directed toward a target (tennis player's adjustments prior to the stroke). The *supplementary motor cortex* has a significant role in the programming of patterns and sequences of movements. For example, electrical stimulation of this area activates complex patterns of movements not only of the contralateral limbs but of the ipsilateral limbs as well. The premotor cortex and the supplementary motor cortex project some fibers to the primary motor cortex.

Two additional coextensive motor and somatic sensory areas are present. In both, direct stimulation produces a somatotopic arrangement of motor responses as well as somatic sensations. These are the *second motor area* and *secondary somatic sensory area*

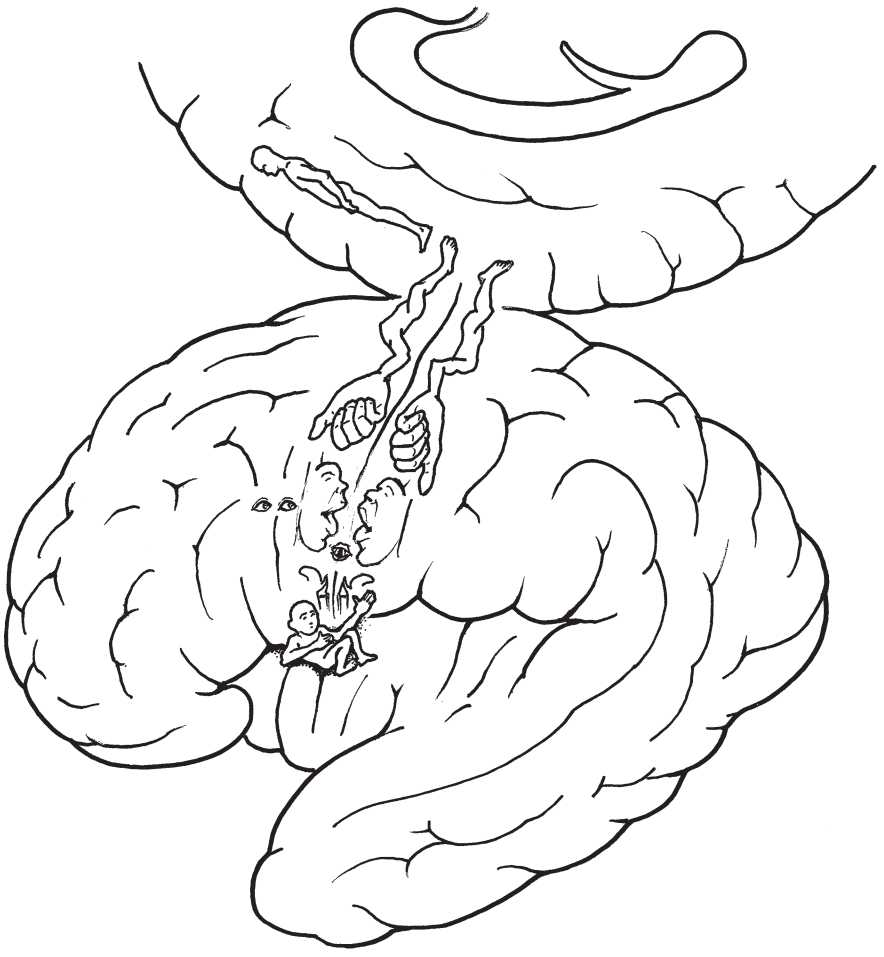


Figure 25.4: The multiple homunculi in the cortex include those in the primary somatic sensory cortex (SI), primary motor cortex, supplementary motor cortex, and combined secondary somatic sensory cortex (SII) and second motor area.

located at the base of the precentral and postcentral gyri (*see* **Fig. 25.3**). All four of the motor areas contribute fibers to the descending motor pathways, including the pyramidal tract.

Stimulation of area 8 results in conjugate saccadic movements of the eyes to the opposite side. This *frontal eye field* mediates voluntary eye movements (called *eye movements on command*; Chap. 19).

Motivation and Control of Movement

In a broad context, the initiation and regulation of volitional movements involves (1) motivation and (2) control. Although how and where movements are initiated is, as yet, unknown, it is probable that those related to *motivation* are generated within the limbic system and that *control* is in the province of the basal ganglia. Following this concept, the drive and behavioral states expressed as motivation activate the neural circuits involved with the actual control of motor activity (Chap. 24). The processing centers where the linkage between the limbic system and the striatal system is thought to occur is in the basal forebrain, probably the *ventral striatum* (nucleus accumbens) and *ventral pallidum*. These components of the basal ganglia through their connections with the amygdala, hippocampus, ventral anterior, and dorsomedial thalamic nuclei have ties with the limbic system (Chap. 22). Functionally, a distinction between motivation and control is expressed in patients with abnormal movement disorders (e.g., choreas and Parkinson's disease). In these individuals, motivation is intact and intense, but execution is faulty.

SENSORY AREAS OF THE NEOCORTEX

General Somesthetic Cortex

The primary somatic sensory (somatosensory) cortex (SI) includes the postcentral gyrus and its medial extension in the paracentral gyrus (areas 3, 1, and 2 of the parietal lobe) (*see* **Figs. 25.3 and 25.5**). Area 3 is subdivided into 3a (located within the posterior bank of the central sulcus in continuity with area 4 on the anterior bank) and 3b. This region receives input from the ventral posterior nucleus of the thalamus, which conveys influences mostly from the opposite side of the head and body. The projection to this area can be represented somatotopically as an upside-down sensory homunculus, with the head located ventrally near the lateral sulcus and the lower extremity in the paracentral gyrus (*see* **Fig. 25.4**). It is clear from **Fig. 25.4** that the greatest representation is given to input from the face, tongue, lips, and hand, especially the thumb and index finger.

The cortical map of areas 3, 1, and 2 (postcentral gyrus) comprises detailed somatotopically organized modality-specific columns that represent various submodalities. Area 3a receives information from muscle spindle afferents and is closely related to the adjacent motor cortex. Somatosensory cortex is hierarchically organized. Area 3b gets input from both rapidly and slowly adapting cutaneous receptors important for determining features such as size, shape, and texture and distributes this information to areas 1 and 2 for further processing. Thus, area 1 receives input from area 3 as well as from rapidly adapting cutaneous receptors, and it mediates perception of textures. The input to area 2 is from area 3 and deep pressure receptors; it serves to differentiate the size and shape of objects and position of joints. In essence, each of these areas has a complete sensory homunculus, reflecting different response properties. The postcentral gyrus also is associated with the characterization of pain and temperature, but these modalities have only a slight representation here. Following unilateral lesions to the primary somatic sensory cortex, sensations of touch, position sense, and pressure are impaired on the contralateral side of the body, but pain and temperature, except for their localization, are, at most, minimally affected.

The secondary somatic sensory area (SII) is located on the superior bank of the lateral fissure below the primary motor and sensory

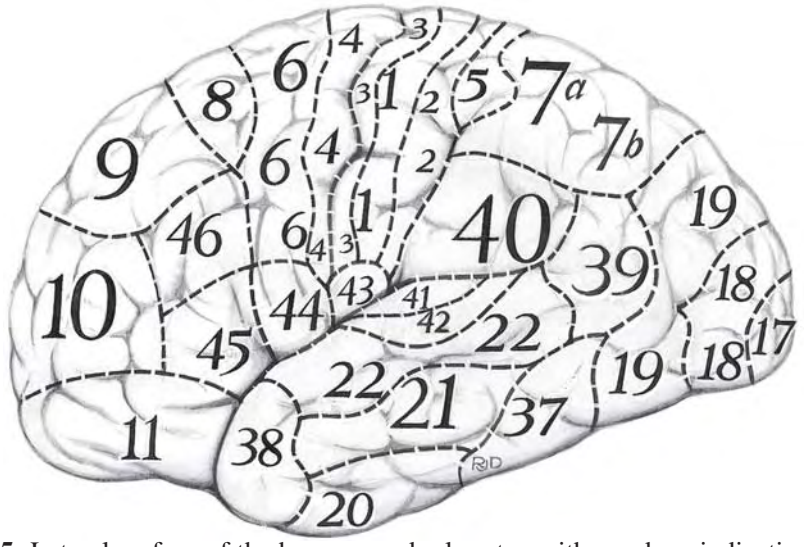


Figure 25.5: Lateral surface of the human cerebral cortex with numbers indicating the areas of Brodmann.

areas. SII is topographically organized with respect to such general sensory modalities as touch, position sense, pressure, and pain. This area receives input from SI as well as bilateral inputs from the ascending pathways.

Further neural processing of the multisensory somesthetic input takes place before being integrated into the levels where perception of shape, size, and texture and the identification of objects by contact occur (e.g., stereognosis—recognition of an object, such as a key or fork, after handling it). This is accomplished in the association areas of the superior parietal lobule (sensory areas 5 and 7) and in the supramarginal gyrus (area 40). These areas have well-developed reciprocal connections with the pulvinar of the thalamus. Lesions in area 40 can result in tactile agnosia (*see* below). Functional activity of this area is essential for the perception of the general senses. Areas 5, 7, and 40 of the parietal lobe comprise the *somatosensory association cortex.*

Electrical stimulation of SI can evoke *paresthesias* (numbness and tingling) and pressure sense from the corresponding part of the body. A lesion of SI results in deficits in position sense and in the ability to discriminate size, shape, and roughness by touch on the contralateral side of the body.

Gustatory and Vestibular Cortices

Taste is represented in area 43, located just above the lateral fissure. Two areas are associated with the vestibular system—one located adjacent to the face area of SI and the other on the superior temporal gyrus adjacent to the primary auditory cortex. The feelings of dizziness and rotation occur during direct electrical stimulation of these areas.

Visual Cortex

The primary visual cortex (area 17), also known as visual area I, is the striate area of the occipital lobe (*see* **Figs. 25.5 and 25.6**). It occupies both banks of the calcarine sulcus and is the cortical terminus of the optic radiations from the lateral geniculate body of the thalamus (Chap. 19). The two principal roles of the striate cortex are (1) to perform the act of fusion of the inputs from both eyes into one image for binocular vision and (2) to analyze the visual world with respect to the orientation of stimuli in the visual fields. Simple and complex cells are localized within the striate cortex;



Figure 25.6: Medial surface of the human cerebral cortex with numbers indicating the areas of Brodmann.

they detect straight lines, each having a specific orientation and position in the retina. The visuotopically organized striate cortex contains ocular dominance columns and orientation preference columns (Chap. 19).

The extrastriate association cortex includes visual area II (area 18), visual area III (area 19), angular gyrus (area 39), and inferotemporal cortex (areas 20 and 21) (*see* **Figs. 25.5 and 25.6**). Actually, almost 40 separate visual areas have been identified. Complex and hypercomplex cells are found within visual areas II and III (Chap. 19). Complex cells respond optimally to linear environmental stimuli, whereas hypercomplex cells respond optimally to curvatures or angular changes in the direction of a line. Lesions in area 39 of the dominant hemisphere can result in patients being unable to comprehend the symbols of language and express themselves through them. This area is essential to the comprehension of a visual image. These association areas are integrated with the "psychical cortex" (*see* below) and the thalamus (pulvinar) through reciprocal connections. As yet, the manner in which visual images are perceived is unknown, but clearly different areas are important for perception of different kinds of visual information.

Through corticotectal fibers, the so-called occipital eye field of areas 18 and 19 mediate slow pursuit and vergence eye movements (Chap. 19). Electrical stimulation of the former results in a conjugate eye movement to the opposite side.

The *inferotemporal cortex* of the tectal system (Chap. 19) has a role in higher visual functions. It reacts to such stimulus features as size, shape, contrast, and color. Monkeys with inferotemporal cortical lesions demonstrate a deficit in the performance of some visual discrimination tasks.

Auditory Cortex

The primary auditory cortex (area 41) is located in the temporal lobe in the transverse gyri of Heschl on the floor of the lateral fissure (*see* **Fig. 25.3**). It is the cortical terminus of the auditory radiations from the medial geniculate body (Chap. 16). Neurons in this area respond to broad bands of the audible spectrum; it is tonotopically organized. The primary cortex is essential for the detection of changes in pattern

and in the location of the source of a sound. Auditory area II (area 42) has a higher threshold to sound intensity than the primary cortex. There are at least five auditory cortical areas in the temporal lobe, including area 22 of the superior temporal gyrus. Patients with lesions of area 22 on the dominant side have profound difficulty in the interpretation of sounds; the spoken language might be meaningless or extremely difficult for them to comprehend.

Plasticity in the Structure of Cortical Columns

A basic question in neurobiology concerns whether synaptic connections in the adult nervous system are static or dynamic. There is direct evidence that neural connections are dynamic in response to functional circumstances. It has been amply demonstrated that the organization of the neocortex in perinatal animals is determined in part by its input from peripheral receptors. For example, Woolsey and his collaborators showed that removal of a mystacial vibrissa (whisker) from a neonatal rodent prevents development of a cortical structure referred to as a barrel in a specific location. A barrel is a circular aggregation of neurons in lamina IV that forms part of a column representing a particular receptive field. Similarly, evidence indicates that the structural organization of adult primate neocortex exhibits changes in response to alterations in its input. Merzenich has shown electrophysiologically that the cortical receptive field of adjacent fingers, which is spatially completely separated under normal circumstances, in time becomes overlapping after the two fingers are surgically joined together (syndactyly). If the fingers are subsequently separated, the cortical representation ultimately reverts to the original discontinuous condition. Merzenich also has demonstrated in monkeys that the cortical representation of a single digit expands with repeated use of that finger. Evidence from human amputees suggests an even more extensive cortical reorganization in which the area representing the face expands to include the adjacent area that had represented the missing limb (Ramachandran et al., 1992). A competitive balance is continually taking place within and between cortical columns in which changing cortical inputs are associated with collateral sprouting and the loss, additions, rearrangement, and alterations of synaptic connections.

Plasticity, at the cortical level, can, in part, explain the increased functional capability of the feet and toes in performing complex motor acts in cases where the arms fail to develop, or the enhanced acuity in one sensory system when another is rendered dysfunctional. It is functionally significant that brain damage at an early age is less deleterious than similar lesions in adulthood.

HIGHER CORTICAL ASSOCIATION AREAS

Language Circuitry

A Conceptual Model for Language and Speech. The cortical areas associated with language are conceived as being organized following a model proposed by Geschwind, which elaborated on circuitry diagramed in 1874 by Wernicke (*see* **Fig. 25.7**). According to this scheme, neural channels originating in the sensory association areas (visual, somatic sensory, and auditory) coalesce at *Wernicke's area (posterior language area)* located in the posterior portion of area 22, which occupies parts of the superior and middle temporal gyri. Some authors also include the supramarginal (area 40) and angular gyri (area 39). This entire region is part of the parieto–temporal–occipital association cortex. Area 22 is critical for the processing of the basic elements for the production of language. Representations visualized as words or images are conveyed from the visual cortex (occipital lobe) to the *angular gyrus* (area 39). Constructs of form, size, and body image are projected from the somatosensory cortex (parietal lobe) to the *supramarginal gyrus* (area 40). Auditory information of sounds and words is thought to be conveyed from the auditory cortex (temporal lobe) to the *angular gyrus* (area 39). Information then is

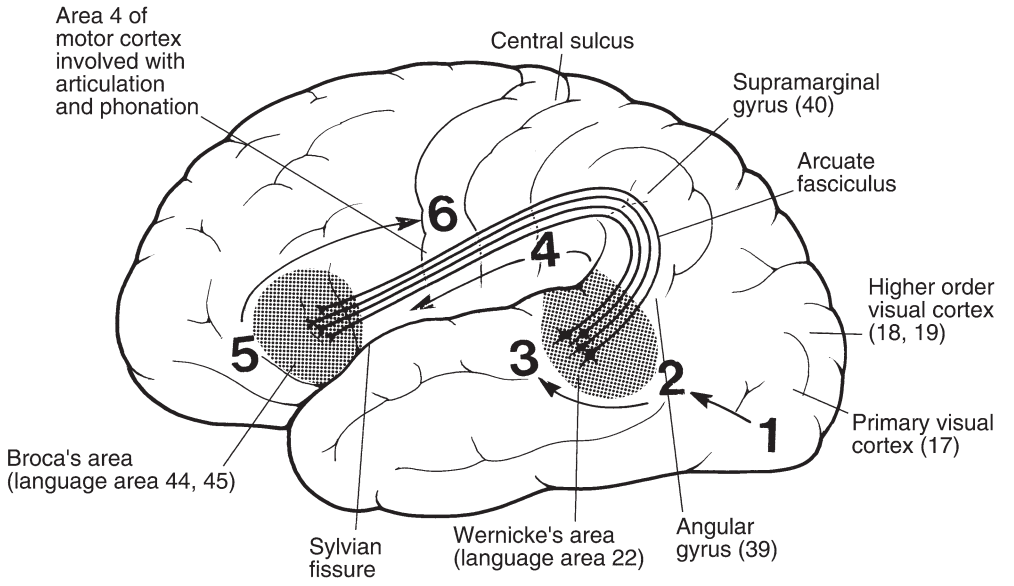


Figure 25.7: Probable sequence of neural transmission within the neocortex that occurs from the perception of an object within the visual areas to the formulation of the spoken language (i.e., naming an object seen). The presumed sequence comprises (1) the visual cortex (areas 17, 18, and 19) to (2) the angular gyrus (area 39) to (3) Wernicke's area (area 22) via (4) the arcuate fasciculus to (5) Broca's speech areas 43 and 44, and, finally, (6) to the motor area 4, where the descending motor pathways involved with vocalization originate.

conducted to area 22. In essence, sensory systems converge on Wernicke's area for further processing.

The words to be spoken originate and are generated in *Wernicke's area* and then transmitted via the arcuate fasciculus to Broca's speech area (*anterior language area;* areas 44 and 45 of the inferior frontal gyrus). Within Broca's area, a detailed coordinated program for vocalization is formulated and activated for controlling articulation through the sequencing of the musculature of the vocal cords, pharynx, tongue, and lips. This information is then transmitted to the motor areas (areas 4 and 6), where the appropriate motor pathways are activated for the production of the spoken language. Key elements of this circuitry have been demonstrated with PET, which also shows that the scheme is oversimplified (*see* **Fig. 25.8**). With regard to language and speech, the left hemisphere of the brain assumes the critical role in about 95% of individuals (left hemisphere dominance) and the remaining 5% have either a right hemisphere dominance or a mixed right and left dominance (*see* later.

Aphasias (*see* Fig. 25.7)

Aphasia, or the disruption of language or speech, can occur following a stroke involving the cortex of the left (major) hemisphere. *Language* is the body of words and systems and their combinations used and understood by groups of people, whereas *speech* refers to facility in the formulation of language. There are several forms of aphasias.

Wernicke's or receptive aphasia results from a lesion of Wernicke's area. Although hearing and vision are normal, individuals with this disability show an essentially total failure to comprehend either spoken and/or written language. Speech of such patients has the correct rhythms and normal nuances of articulation,

but conversations are devoid of content and full of nonsense words. Their speech is fluent but meaningless. Afflicted subjects seem unaware that their speech is meaningless. Thus, *Wernicke's area* has an important role in the mechanisms of language, including reading, writing, and the production and comprehension of the spoken word.

Conduction aphasia results from lesions in the lower parietal lobe that damage the fibers of the *arcuate fasciculus* that connect Wernicke's area to Broca's area. In individuals with this *disconnection syndrome*, speech is fluent but quite meaningless. They show a poor ability to repeat phrases and spoken language.

Anomia aphasia occurs following a lesion of the posterior portion of the left superior temporal gyrus near the angular gyrus. Patients demonstrate an inability to think of a specific word or the name of a person or an object. In a lesion limited to the angular gyrus, patients might lose the ability to read (called *alexia*) or to write (*agraphia*) even though they can understand the spoken language and can speak. These lesions interfere with the transfer of information from the visual (occipital lobe) and general somatic sensory (parietal lobe) cortices to Wernicke's area.

Global or *total aphasia* is associated with widespread damage of the cortex on either side of the lateral (Sylvian) sulcus, damaging Wernicke's and Broca's areas and the arcuate fasciculus. Such patients are unable to speak or comprehend language. In addition, they have a severe impairment of language-related functions in that they cannot read, write, or name an object.

When *Broca's area* on the left side is damaged by a stroke, Broca's aphasia (*expressive aphasia*) can result. It is primarily a failure in the formulation of speech, which is labored, slow, and poorly articulated. Patients have great

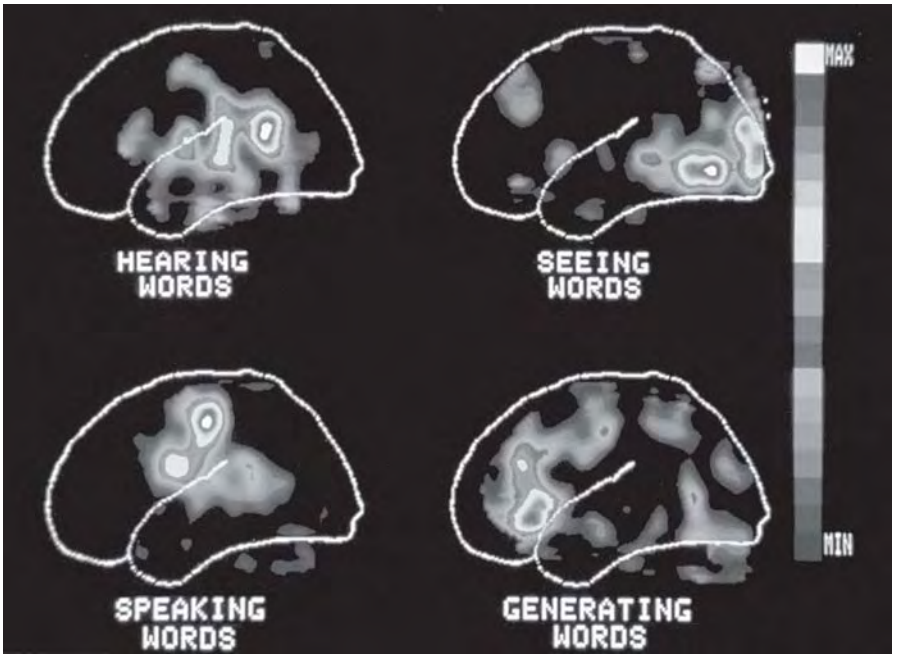


Figure 25.8: Positron-emission tomographs show areas with increased blood flow elicited by language-related activities. Note the relationships between these areas and those illustrated in Figure 25.7, including Wernicke's area. (Courtesy of Dr. Steve Petersen and Dr. Marcus Raichle, Washington University.)

difficulty expressing themselves. They are fully aware of the disability. The muscles involved with speech are not paralyzed, demonstrated by the fact that they function normally in other tasks such as chewing, swallowing, and laughing. Many patients can often sing a formerly known song rapidly, correctly, and even with feeling. In responding to a question, a patient gives a comprehensible answer, but it is expressed with difficulty and with the omission of small words ("a" and "the") and endings. It might be delivered in a disjointed style. The comprehension of written matter and the ability to write are unimpaired.

Agnosias

Agnosia (*Greek,* lack of knowledge) refers to an inability to recognize or to be aware of an object when using a given sense (sight) even though this sense is essentially functionally intact.

Tactile agnosia (astereognosis), the inability to recognize familiar objects through the senses of touch and proprioception, can result from lesions of the *supramarginal gyrus (area 40)* of the major hemisphere. Patients with tactile agnosia might have a disturbance of the body image; for example, they might not recognize their individual fingers and might confuse the left from the right side of the body.

Visual agnosia, the inability to recognize objects by sight, can result from a lesion in areas 18 and 19 of the major hemisphere. These individuals are able to characterize the objects by the use of other senses such as touch.

Auditory agnosia, the inability of an individual with unimpaired hearing to recognize familiar sounds, music, and words, results from bilateral lesions in the posterior parts of the superior temporal gyrus (area 22). Such patients have reasonable ability to comprehend the spoken language and show good reading ability.

Apraxia

Apraxia is the inability to perform certain skilled and complex movements, even though there is no paralysis or disturbance in motor coordination and the sensory pathways are functioning normally. Lesions in various cortical areas (supramarginal gyrus, other regions of the parietal and occipital lobes, premotor cortex, and Broca's speech areas 44 and 45), the association fibers interconnecting many of these cortical areas, and in the corpus callosum can result in several types of apraxia. Among these are (1) an inability to perform skilled learned movements, ranging from the clumsy execution of writing and drawing to *agraphia*, a condition in which the subject cannot write, (2) an inability to carry out a sequence of complex motor acts (often called *transmissive apraxia*) (e.g., subjects who are able to brush their teeth, comb their hair, wash their fac,e and tie their shoes automatically, are unable, upon command, to perform the same tasks in a specified sequence [lesion in the supramarginal gyrus]), and (3) the loss of articulate speech (sometimes called *oral aphasia*) with otherwise normal musculature of the tongue, lips, larynx, and palate. Subjects have use of only a few words in conversation and mispronounce common words or repeat them over and over again (lesion in Broca's areas 44 and 45 and in other regions).

Prefrontal Cortex

The prefrontal cortex (areas 9 through 12) and its rich reciprocal connections with the dorsomedial nucleus of the thalamus, hypothalamus, and limbic system are well developed in man. The prefrontal lobe has been conceived as being a regulator of the depth of feeling of an individual. It is not involved in the perception of sensations, but, rather, in the "affect" associated with sensations. The complex responses of an individual, from calmness to ecstasy, from gloom to elation, from friendliness to disagreeableness, have their roots in areas 9 to 12.

The bilateral ablation of areas of the prefrontal cortex or interruption of the subcortical white matter (*prefrontal lobotomy, leukotomy*) can produce subjects who are less excitable, but also less creative. Relief from anxiety is accompanied by a change in the patient's outlook and disposition. Drive, not intelligence as

measured by IQ tests, is altered. Goal-directed activity and planning for the future are disturbed and generally neglected. The ability to remember information such as a sequence of numbers for a short period (*"working memory"*) is impaired, particularly when lesions involve dorsolateral parts of the frontal lobes. The landmark case of Phineas Gage exemplifies the above. Gage was a foreman working on a project to lay track for the Rutland and Burlington Railroad in Vermont, when, in 1848, a tamping iron was blown through his head, producing a prefrontal lobotomy. Only transiently stunned, he survived for some 12 years. Although his brain was not recovered, the skull was preserved and recent reconstructions with neuroimaging techniques have confirmed that the prefrontal areas were damaged bilaterally, particularly medial and ventral parts; other parts of the frontal lobes (i.e., Broca's area and areas 6 and 4) were spared. His personality changes were so profound that friends said "Gage was no longer Gage." Whereas he was physically as before and showed no apparent changes in memory, learning, or intellect, he became profane and irresponsible to the point of being unable to hold down a job.

There is support for the view that some of the expressions are, at least in part, associated with interactions between the locus ceruleus, prefrontal lobe, and limbic system. The locus ceruleus, with adrenergic projections, imposes excitatory influences on both the prefrontal cortex and the limbic system. In turn, the prefrontal cortex, through its inhibitory influences, modulates the activity of the limbic system. Thus, following prefrontal lobotomy, the limbic system, now partially released from some prefrontal constraints, has freer rein for expression.

The perception of pain includes both the sensation of pain and the emotional reaction to it. The neospinothalamic or fast pain pathway, involving the somatosensory cortex, is the warning system informing the individual of the presence, extent, and location of an injury causing the pain. The paleospinothalamic or slow pain pathway involves the unpleasant and nagging qualities, and signals that normal activity should be curtailed and attention should be paid to the pain. The "fast" system is relatively "free of emotional content," whereas the slow system contributes to the emotional quality of the insult. Both the limbic system and the prefrontal lobes contribute to the emotional coloration of the pain.

Relief from intractable pain can be obtained following prefrontal lobotomy. Although the pain persists, the patient is unconcerned because the psychic feeling associated with its intensity is lost. Data show that the prefrontal cortex is the neocortical representative of the limbic system.

BLOOD FLOW IN THE CORTEX

The mean blood flow in the brain of normal individuals is 50 mL per 100 g of tissue per minute. However, at any given moment, the blood flow through a specific region might be greater or less than the mean, as illustrated in **Fig. 25.8**. The brain is similar to other body tissues in that the blood flow varies with the level of metabolism and functional activity within the tissue. An increase in blood flow takes place, for example, in the primary and association auditory cortices (areas 41 and 42) in both hemispheres and in Wernicke's areas in the left hemisphere during a conversation. Dynamic movements of the hand evoke blood flow increases in several cortical areas involved with hand movements and with sensory signals in the skin, joints, and muscles associated with the movements. Blood flow increases occur in the contralateral "hand" region of the motor cortex (area 4) and postcentral gyrus (somatosensory cortex) and of both ipsilateral and contralateral premotor and supplementary motor cortices (areas 6 and 8). The motor and sensory activities involved with the acts of reading aloud and listening result in an increase of blood flow in both the ipsilateral and contralateral auditory cortices, motor and somatosensory cortices ("face" and "mouth" areas), premotor and supplementary motor cor-

tices, Broca's speech area, frontal eye fields (area 8), and visual association cortices of both sides.

SPLIT-BRAIN MAN AND CEREBRAL DOMINANCE

The presence in the cerebrum of the corpus callosum, with its 300 million fibers in humans, and of the anterior commissure suggests that interhemispheric commissural fiber pathways are of crucial functional significance. Most of the callosal fibers interconnect with mirror-image sites of both hemispheres. In addition, many fibers terminate in cortical areas different from the areas of origin (e.g., area 17 of one hemisphere projects to areas 18 and 19 of the other). Several areas do not receive callosal fibers; these include the hand and foot areas of the primary motor cortex (area 4), second motor area, somatosensory cortex (SI and SII), and primary visual cortex (area 17). The commissural fibers to and from the temporal cortex, particularly the middle and inferior temporal gyri, pass through the anterior commissure (*see* **Fig. 1.7**). In essence, the cortices of the two hemispheres are in continuous communication with each other through the fibers of the corpus callosum and anterior commissure.

Yet, when the corpus callosum is completely transected, no functional alterations can be detected by the usual neurologic and psychologic examinations. Complex activities, such as playing musical instruments and writing, are performed with the same dexterity as before surgery.

An experimental animal or human being with the corpus callosum and other commissures (anterior and hippocampal commissures) transected has, in a way, two brains; the term *twin brain* or *split brain* applies. They behave normally, are alert and curious, perceive, learn, and retain learned activities.

Studies of split-brain monkeys and human beings have been conducted whereby the input from the periphery is projected to only one hemisphere. The memories of perceptually learned information and of learned motor activities are apparently confined to the hemisphere to which the sensory information was relayed and from which the motor output was projected. If the corpus callosum is intact, this memory is utilized for motor expression by both hemispheres. Apparently, the *engram*, or *memory trace*, laid down in the directly trained hemisphere is transferred via the callosal fibers to the opposite hemisphere, and a second engram is created in the contralateral hemisphere.

In common usage, dominance as applied to a hemisphere is imprecise, as each hemisphere is dominant for certain functions (*see* **Fig. 25.9**). For example, the left hemisphere is dominant for language and the right hemisphereis dominant for spatial construction (stereognosis). Neither hemisphere should be regarded as subordinate overall. The "dominant" hemisphere is also called the *major hemisphere* and the "nondominant" hemisphereis also called the *minor hemisphere*. In most individuals, the major hemisphere is the left hemisphere and the minor hemisphere is the right hemisphere.

In human beings, speech and the language symbolisms of the written and spoken word are lateralized in the major hemisphere. Both the major (or "talking") hemisphere and the minor ("mute") hemisphere can comprehend, but normally only the major hemisphere "talks". Linguistic expression resides exclusively within the major hemisphere, whereas the comprehension of both the written and spoken language is represented in both hemispheres.

The minor hemisphere can perceive tactile, auditory, and visual information, but is unable to communicate through verbal language. However, it can respond and communicate by gestures (e.g., pointing) or emotional activity (e.g., fidgeting or blushing). The minor hemisphere is specialized to appreciate spatial dimensions, to grasp the totality of a scene, and to recognize the faces of people better than the major hemisphere. This mute hemisphere is presumed to have an essential role in creative acts associated with musical, poetic, and imaginative expressions.

Human split-brain subjects exhibit some interesting and curious disturbances of higher brain function. When these result from lesions of the corpus callosum or of cortical association areas giving rise to commissural fibers, they are known as *disconnection syndromes*.

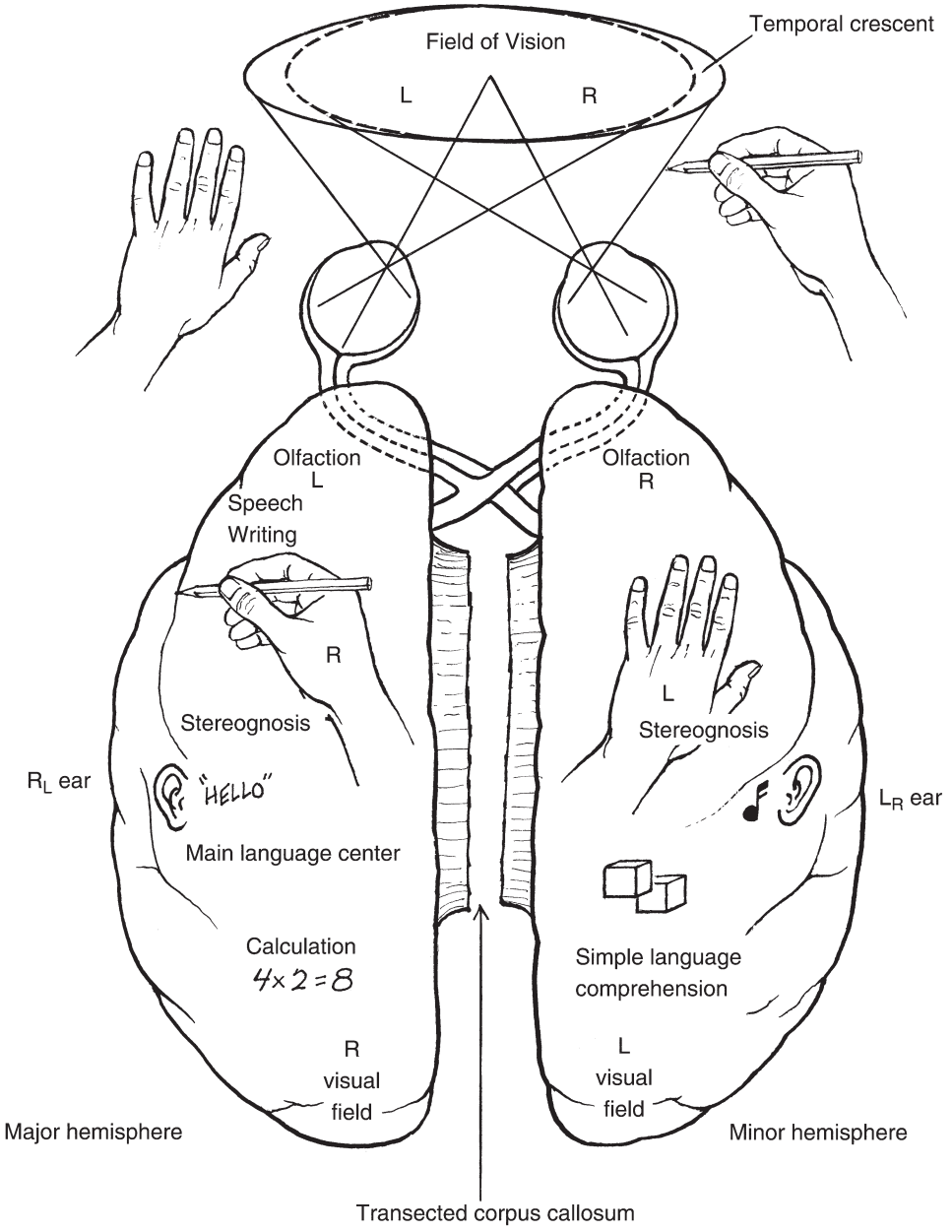


Figure 25.9: Some of the roles of the major and minor cerebral hemispheres as established in "twin-brain" humans. General senses from one hand and from half of the visual field are projected to the contralateral hemisphere. The olfactory sense is conveyed to the ipsilateral hemisphere. Hearing is largely projected to the contralateral hemisphere. (Adapted from Sperry, 1985.)

The ultimate expression of the general sensory information conveyed from the right hand to the left or major hemisphere can differ dramatically from that which is conveyed from the left hand to the right or minor hemisphere. The right hand might be "unaware" of what the left hand is doing; for example, the right hand might be buttoning a shirt while the left hand is unbuttoning it. The subject can name an object held in the right hand, but cannot name an object held in the left hand; the act of naming is a function of the major hemisphere. These patients can perform certain tasks better with the left hand than with the right hand. This indicates that the minor hemisphere does have some superior roles over the major hemisphere. For example, better performances are executed by the left hand than by the right hand in tasks involving spatial relations such as arranging blocks, drawing simple three-dimensional objects (cubes), and matching up designs.

Several basic conclusions concerning the roles of the cerebral hemispheres obtained from studies of "twin-brain" subjects (*see* **Fig. 25.9**) are that (1) perception and memory can be performed independently in both hemispheres, (2) language and speech are almost exclusively the roles of the major hemisphere, (3) the minor hemisphere is superior to the major hemisphere in the recognition and appreciation of spatial dimensions, (4) the primary role of the cerebral commissures is in the bilateral integration of the two hemispheres for linguistic functions, (5) it is through the major hemisphere that humans can express thoughts and knowledge through language, and (6) the commissures are essential for maintaining the unity of the higher sensory and motor functions of the cerebrum. The following is a rather simplistic summary of the roles of the two hemispheres. The left (major) hemisphere can be considered to be the analytical, rational, and verbal half of the cerebrum. It is analytic, as used in language recognition. The right (minor) hemisphere is the synthetic, intuitive, and nonverbal half. It is nonanalytical and used in perceptive recognition.

The lateralization of Broca's speech area is not causally related to handedness. Actually, speech functions are lateralized to the left hemisphere in most adults regardless of hand preference. Roughly 80% of adults are right-handed, 10% are left-handed, and 10% are ambidextrous. In right-handers, the left cortical motor areas control the right hand, whereas in left-handers, the right cortical motor areas control the left hand. About 90% of right-handers have speech centers in the left hemisphere, and the other 10% have speech centers in the right hemisphere. About 65% of left-handers also have speech centers in the left hemisphere, 20% in the right hemisphere, and the remaining 15% have speech centers located bilaterally. Naturally ambidextrous subjects have their speech centers located as follows: 60% in the left hemisphere, 10% in the right hemisphere, and 30% in both hemispheres.

In general, injuries of the brain in infants and children are often accompanied by less severe neurological impairment and greater recovery of function (expression of more plasticity) than similar injuries in the adult. This "infant lesion effect" is dramatically demonstrated following unilateral damage to the cerebrum. In a child, after extensive cerebral damage as a consequence of a cerebral infarction or hemispherectomy for relief from intractable seizures, there is marked compensatory recovery of functional deficiencies. The intact hemisphere can assume the ability to perform many of the impaired skilled movements and language functions.

MEMORY

Learning and memory are expressions of neuronal processing. *Learning* is the means by which we realize new knowledge and perceptions about events and experience. *Memory* is characterized as the consequence of the acquisition, storage, and recall of previously learned experiences.

A general framework of neuronal circuitry of both parallel and hierarchical components relevant to memory in the primates, including humans, was proposed by Mishkin and Appen-

zeller (1987). The presence and presumed roles of different parts are based on studies of neurologic patients with impaired memories and of primates with selectively placed lesions (Squire and Zola-Morgan, 1988, and others). In essence, the sequence of feed-forward processing connections and their functional correlates in the cerebral cortical and subcortical circuits leading to memory (1) commences with sensory association cortical areas, (2) proceeds through channels converging to the neocortex of each anterior temporal lobe, (3) continues to the parahippocampal cortex and its projections to the amygdala and hippocampus, (4) proceeds via their diffusely distributed circuits including the basal forebrain area, and, finally, (5) completes the "circle" with projections from the basal nucleus of Meynert to broad areas of the neocortex (*see* **Fig. 25.10**).

Neuronal channels comprise pathways from the visual, auditory, and somatic sensory association areas (including angular gyrus, supramarginal gyrus) that converge to the cortex of the anterior temporal lobe (*see* **Fig. 25.10**). Each of these pathways consists of a number of converging and diverging processing channels and subsets of neuronal pools. Each subset is involved with a specific visual, auditory, or somatic sensory feature or combination of features.

There are two pathways from primary visual cortex: (1) One pathway consists of processing sequences directed toward the temporal lobe. It is involved with the "broader context" of the visual world. Its neurons respond to such environmental stimuli as shape and color basic to "object vision." A portion of the superior temporal gyrus has a role in analyzing visual motion related to the subjective perception of movement during a visual task. (2) Another pathway directed toward the posterior temporal lobe is involved with visual attention and the spatial relations of the object or the scene observed. The "spatial system" is associated with the perception of an object in context with the other landmarks in the visual field, so-called object and pattern discrimination. This pathway is thought to interact with tactile channels from the parietal lobe cortex (cross-modality interactions). Other cortical pathways conveying information from the auditory, somatosensory, and gustatory association areas converge in the anterior temporal neocortex.

Neurons in anterior temporal lobe neocortex are responsive to a wide variety of features of the visual, auditory, tactile, and taste spheres. They integrate these diverse inputs from the world, which bombard the individual. Confirmatory evidence has been obtained from electrical stimulation of this cortex in conscious patients that can evoke associations relative to "experiences" (Thompson and Krupa, 1994). It can also elicit the recall of objects seen, music heard, or objects touched. Visual and auditory hallucinations can be produced, such as a clear re-enactment of an experience of the recent or distant past. The evoked experiences might be a symphonic melody that the subject thinks is being played on a phonograph or radio. The patient with temporal lobe tumors might have auditory or visual hallucinations and see vivid scenes and friends not present and hear songs not sung. The patient is cognizant of the hallucinations that are consistent with experiences seen or heard in the past (deja vu). In a sense, a neuron or small group of neurons in this area are "windows to our internal and external worlds."

From this temporal lobe, cortex channels project to the limbic lobe cortex on the medial aspect of the temporal lobe (parahippocampal gyrus and subiculum). Reciprocal circuits interconnect the medial temporal lobe cortex with two major processing structures, the amygdala and the hippocampus, which are part of the limbic system. The amygdala also receives direct input from the olfactory system.

Bilateral removal of the medial portions of the temporal lobes, including the amygdala and hippocampus result in severe memory deficits (even total amnesia), specifically with a loss of capacity to consolidate or retain *short-term (recent) memory*. Thus, these patients lose the capacity to form and to store new long-term memories; however, long-term memories acquired before surgery remain essentially

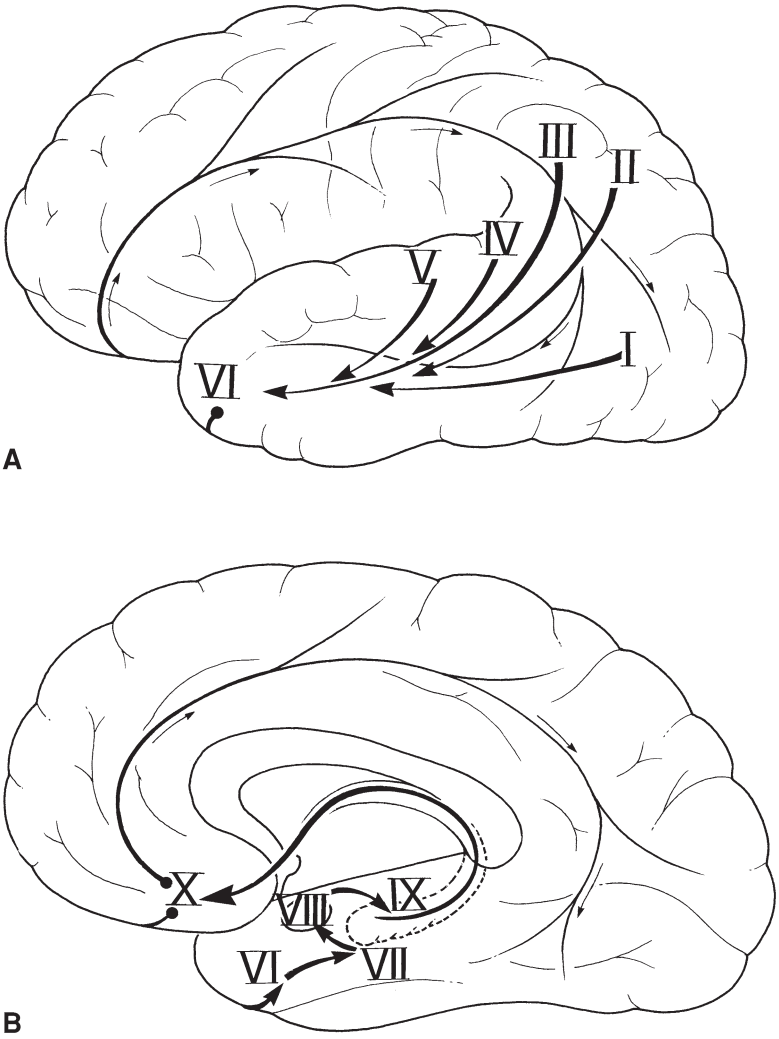


Figure 25.10: Possible sequence of neural transmission that is involved with the formulation of memory. **(A)** Neocortical pathways converge from the sensory association areas via several neural circuits to the neocortex of the anterior temporal lobe. These circuits include the (I) "broader concept" visual pathway from the occipital lobe, (II) "spatial" visual pathways from the posterior parietal lobe, (III) somatosensory pathways from the parietal lobe, (IV) auditory pathways from the temporal lobe, and (V) the gustatory pathways from the superior temporal lobe cortex. These pathways converge to the anterior temporal lobe cortex (VI). **(B)** From the anterior temporal lobe cortex, information is conveyed (VI) to the subiculum and parahippocampal gyrus of the paleocortex (VII). From this paleocortex, circuits project to the amygdala (VIII) and hippocampus (IX), both of which project widely (Chap. 22) to the basal forebrain area, including the basal nucleus of Meynert (X). In turn, projections from the basal area "complete" the overall circuitry via fibers from the basal nucleus of Meynert back to the neocortical sensory association areas somehow to fix a new memory or to elicit an old memory. "Working memory" (memory retrieved and temporarily held) is extracted from "long-term memory" that is consolidated, dispersed, and stored at multiple sites in the brain.

intact and can be recalled, often vividly, many years later. As generally used, short-term memory comprises the information and awareness that one retains for only a short time-span. Unilateral removal of the amygdala and hippocampus does not result in impairments of memory (*see* Klüver-Bucy Syndrome, Chap. 22).

This region of the temporal lobe has great importance in learning and memory functions. The hippocampus is an essential component in establishing memory. Amnesia ensues following bilateral lesions of the hippocampus and surrounding cortical regions that spare the amygdala. These observations indicate that the ablated structures are in some way involved with the consolidation of memory but not with its storage.

Bilateral ablation limited to the amygdala (monkey) has no detectable effect on memory. The widespread connections that the amygdala has with the neocortex and its strategic location as a major processing center suggest that the amygdala plays a role in the modulation of incoming sensory information. In addition, it might be important in establishing associations to events and in correlating information from different modalities. Thus, the amygdala might affect performance of memory tasks that depend on these functions. Another view is that both the amygdala and the hippocampus are essential for *recognition memory* (recognizing an object such as a glass) and *associative memory* (e.g., a glass can be associated with a glass of water or milk, or a bark with the image of a barking dog). The connections of the amygdala with the limbic system, including the hypothalamus, enables sensory events and perceptions to develop emotional associations and expressions (the latter through the autonomic nervous system). Thus, the amygdala can act as an intermediary between the sensory systems and emotions.

As to neural connections, the amygdala has reciprocal circuits with the cerebral cortex, striatum, hypothalamus, brainstem, thalamus, and hippocampus. The hippocampus projects its output via two major efferent circuits (1) via the fornix to the mammillary body and other sites (Chap. 22) and (2) reciprocally to the medial temporal lobe and, hence, via association bundles to the neocortical association areas of the four lobes, especially the prefrontal cortex. Evidence indicates that the hippocampus is implicated in memory mechanisms such as to make it possible for humans to compare the present circumstance with previously experienced events. Lesions of the fornix or of the mammillary bodies (formerly thought to result in amnesia) results in a negligible and transient loss of memory.

Some evidence suggests that the medial thalamus, possibly the medial (dorsomedial) thalamic nucleus, is also involved in the formulation of memory. Bilateral damage of the midline diencephalon can result in profound amnesia in humans and severe memory impairment in monkeys. In essence, the reciprocal neural linkages between the hippocampus and the neocortex are envisioned as being involved in the dynamics of memory. They are involved in the initial phase of learning (e.g., impression of novel image, namely short-term memory). Then, followed by a limited period, the image, if retained, gradually becomes independent of the hippocampus and goes into the *long-term memory* domain.

In general, the hippocampus seems to be more involved with registering cognitive information than with emotion, whereas the amygdala has an essential role in the expression of emotion rather than with cognition.

Another link in the memory channels involves the substantia innominata and the *basal nucleus of Meynert* (Chap. 22; *see* **Fig. 22.2**). This region receives afferent input from the amygdala, insula, and parts of the parahippocampal gyrus; it projects diffusely to such centers as the amygdala, hippocampus, hypothalamus, and some brainstem nuclei. Importantly, the basal nucleus contains cholinergic neurons whose fibers are distributed widely to the entire neocortex in a quite orderly topographic manner and are regarded as a major source of cortical acetylcholine. Its neurons have excitatory synapses with muscarinic receptors of cortical neurons. This nucleus is

thought of as acting as the final linkage (along with the output of the hippocampus to many areas of the neocortex) to close the loop that is involved with the processing and storage of acquired information (the "stored memories in the neocortex"). One concept postulates that this link in the loop evokes changes in the neurons and local circuits of the sensory areas that fix a perception so that it is stored in *memory* and, in addition, possibly releases previously stored memories in the neocortex to our conscious self.

Alzheimer's disease (presenile dementia), as well as senile dementia, which is the same entity except for age of onset, is an affliction with initial signs of forgetfulness leading to progressively more severe mental deterioration. Patients exhibit a loss of memory and become confused and disoriented. They are incapable of abstract thought. In advanced stages, they cannot recognize even close friends and relatives. Diffuse cerebral atrophy, particularly involving the frontal and temporal lobes, is a constant attribute. Alzheimer's disease is a degenerative disease with an established genetic predisposition characterized by having *senile plaques* and *neurofibrillary tangles*. These plaques are found throughout the cerebral cortex and hippocampus. Each plaque is composed of enlarged degenerating cholinergic axonal endings surrounding a core composed mainly of extracellular amyloid. The filaments of the tangles are primarily 20-nm wide components of the tangle. The symptoms might be the result, in part, of the massive destruction of these neurons. Alzheimer patients have reduced neocortical acetylcholine and its precursor enzyme, acetylcholine transferase.

Modular Organization of the Brain

"An emerging view is that the brain is structurally and functionally organized into discrete units or `modules' and that these components interact to produce mental activities" (Gazzaniga, 1989). In a broad sense, the major sensory systems, such as the visual system, are complexes of modular systems. In turn, each system comprises several modules. This is expressed in the visual system, where several anatomically and physiologically documented modules, including cortical areas, are embedded within the system. Each module processes different dimensions of visual information such as color, depth perception, and motion (Chap. 19; Hubel, 1987). Higher degrees of processing within functionally specific anatomic modules of the cerebral cortex involved with memory have been demonstrated in the monkey (noted in this chapter; Mishkin and Apenzeller, 1987). Another complex of modules present in the human brain are those involved with a variety of language processes.

At higher levels, the human brain appears to have a modular organization consisting of identifiable components that participate in the generation of the cognitive state, including the appreciation of the surrounding world and past events, perception, reasoning, and the unitary experience of conscious awareness (Gazzaniga, 1989).

Dynamic Maintenance of Cortical Areas

Cortical areas such as the V4 color area are functionally distinct divisions that are precisely localized. The circuitry of the neuronal organization within each area is (1) nurtured during development by "self-organization" and active neural activity patterns generated by inputs and (2) maintained during adulthood by active dynamic inputs (Kaas, 1987). Hence, cortical maps are shaped and sustained by neural activity.

The micro-organization (local circuitry) of the cortex is in a constant state of flux, depending on a variety of competitive inputs. Stability in a cortical area results from a balance of these inputs. Increased input from greater usage tends to increase the amount of cortical space dedicated to a specific modality, whereas decreased usage tends to decrease its cortical representation (Chap. 6). It is clear that mental activity and physical exercise associated with stimulation derived from sensory receptors and the activation of reflexes and movements exert positive roles in sustaining and maintaining the integrity of cortical areas throughout life.

The preceding has provided merely a brief introduction to the vast topic of cognition, memory, and language about which a vast literature exists. References are provided to guide readers interested in pursuing this subject, which has been moving rapidly since the advent and refinement of functional imaging techniques. Intriguing new insights have evolved since the discovery of what are referred to as "mirror neurons." Mirror neurons, first described in the monkey ventral premotor cortex, which is homologous to Broca's area, "discharge both when the monkey grasps or manipulates objects and when it observes the experimenter making similar actions" (Rizzolati and Arbib, 1998). It is thought that this matching of codes for observation and execution of movements was a crucial precondition for the development of language in that it enabled utterances to have the same meaning for both the speaker and listener. Future studies in this area should prove to be very exciting.

SUGGESTED READINGS

Arbib MA. Language evolution: the mirror system hypothesis. In: *The Handbook of Brain Theory and Neural Networks.* 2nd ed. Arbib MA, ed. Cambridge, MA: MIT Press; 2003:606–611.

Arbib MA, Billard A, Iacoboni M, Oztop E. Synthetic brain imaging: grasping, mirror neurons and imitation. *Neural Netw.* 2000;13:975–997.

Blake DT, Byl NN, Merzenich MM. Representation of the hand in the cerebral cortex. *Behav. Brain Res.* 2002;135:179–184.

Borsook D, Becerra L, Fishman S, et al. Acute plasticity in the human somatosensory cortex following amputation. *Neuroreport* 1998;9:1013–1017.

Brodmann K, Garey LJ. *Brodmann's Localisation in the Cerebral Cortex.* (Translated from 1909 publication with editorial notes and introduction by Laurence Garey.) London: Imperial College Press; 1999.

Damasio AR, Damasio H. Brain and language. *Sci. Am.* 1992;267:88–95.

Damasio H, Grabowski T, Frank R, Galaburda AM, Damasio AR. The return of Phineas Gage: clues about the brain from the skull of a famous patient. *Science* 1994;264:1102–1105.

Douglas R, Keyan AC. Neuronal Circuits of the Neocortex. *Ann. Rev. Neurosci.* 2004;27:419–451.

Ferrari PF, Gallese V, Rizzolatti G, Fogassi L. Mirror neurons responding to the observation of ingestive and communicative mouth actions in the monkey ventral premotor cortex. *Eur. J. Neurosci.* 2003;17:1703–1714.

Funnell MG, Corballis PM, Gazzaniga MS. Temporal discrimination in the split brain. *Brain Cogn.* 2003;53:218–222.

Gazzaniga MS, Ivry RB, Mangun G.R. *Cognitive Neuroscience: The Biology of the Mind.* New York: Norton; 2002.

Gazzaniga MS. Organization of the human brain. *Science* 1989;245:947–952.

Goldman-Rakic PS. The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. *Phil. Trans. R. Soc. Lond. B: Biol. Sci.* 1996; 351:1445–1453.

Goldman-Rakic PS. The cortical dopamine system: role in memory and cognition. *Adv. Pharmacol.* 1998;42:707–711.

Grezes J, Armony JL, Rowe J, Passingham RE. Activations related to "mirror" and "canonical" neurones in the human brain: an fMRI study. *Neuroimage* 2003;18:928–937.

Hamzei F, Rijntjes M, Dettmers C, Glauche V, Weiller C, Buchel C. The human action recognition system and its relationship to Broca's area: an fMRI study. *Neuroimage* 2003;19: 637–644.

Handy TC, Gazzaniga MS, Ivry RB. Cortical and subcortical contributions to the representation of temporal information. *Neuropsychologia* 2003; 41:1461–1473.

Harris JC. Social neuroscience, empathy, brain integration, and neurodevelopmental disorders. *Physiol. Behav.* 2003;79:525–531.

Haxby JV, Petit L, Ungerleider LG, Courtney SM. Distinguishing the functional roles of multiple regions in distributed neural systems for visual working memory. *Neuroimage* 2000;11:145–156.

Hubel DH. *Eye, Brain, and Vision.* New York: Scientific American Library; 1987.

Jenkins WM, Merzenich MM. Reorganization of neocortical representations after brain injury: a neurophysiological model of the bases of recovery from stroke. *Prog. Brain Res.* 1987;71: 249–266.

Kaas JH. The organization of neocortex in mammals: implications for theories of brain function. *Annu. Rev. Psychol.* 1987;38:129–151.

Kelleher RJ, Crowdon JH. Alzheimer's disease. In: Kelleher LH, et al., eds. *Diseases of the Nervous System, Clinical Neuroscience and Therapeutic Principles.* 3rd ed. New York: Cambridge University Press, 2002; 237–251.

Keysers C, Kohler E, Umilta MA, Nanetti L, Fogassi L, Gallese V. Audiovisual mirror neurons and action recognition. *Exp. Brain Res.* 2003; 153:628–636.

Kroll NE, Yonelinas AP, Kishiyama MM, Baynes K, Knight RT, Gazzaniga MS. *The neural substrates of visual implicit memory: do the two hemispheres play different roles? J Cogn Neurosci.* 2003;15:833–842.

Levy R, Goldman-Rakic PS. Association of storage and processing functions in the dorsolateral prefrontal cortex of the nonhuman primate. *J. Neurosci.* 1999;19:5149–5158.

Liu X, Robertson E, Miall RC. Neuronal activity related to the visual representation of arm movements in the lateral cerebellar cortex. *J. Neurophysiol.* 2003;89:1223–1237.

Merzenich M. Cognitive neuroscience. Seeing in the sound zone. *Nature* 2000;404:820–821.

Merzenich MM, Nelson RJ, Stryker MP, Cynader MS, Schoppmann A, Zook JM. Somatosensory cortical map changes following digit amputation in adult monkeys. *J. Comp. Neurol.* 1984;224: 591–605.

Merzenich M, Wright B, Jenkins W, et al. Cortical plasticity underlying perceptual, motor, and cognitive skill development: implications for neurorehabilitation. *Cold Spring. Harbor Symp. Quant. Biol.* 1996;61:1–8.

Miall RC. Connecting mirror neurons and forward models. *Neuroreport* 2003;14:2135–2137.

Miller MB, Van Horn JD, Wolford GL, et al. Extensive individual differences in brain activations associated with episodic retrieval are reliable over time. *J. Cogn. Neurosci.* 2002;14: 1200–1214.

Mishkin M, Appenzeller T. The anatomy of memory. *Sci. Am.* 1987;256:80–89.

Nicolelis MA. Brain-machine interfaces to restore motor function and probe neural circuits. *Nature Rev. Neurosci.* 2003;4:417–422.

Oztop E, Arbib MA. Schema design and implementation of the grasp-related mirror neuron system. *Biol. Cybern.* 2002;87:116–140.

Penfield W, Roberts L. *Speech and Brain Mechanisms*. Princeton: Princeton University Press.

Ramachandran VS, Stewart M, Rogers-Ramachandran DC. Perceptual correlates of massive cortical reorganization. *Neuroreport* 1992;3:583–586.

Rizzolatti G, Arbib MA. Language within our grasp. *Trends Neurosci.* 1998;21:188–194.

Solso RL. *Mind and Brain Sciences in the 21st Century.* Cambridge, MA: MIT Press; 1997.

Squire LR and Schacter DL. *Neuropsychology of Memory.* New York: Guilford Press; 2002.

Squire LR, Zola-Morgan S. Memory: brain systems and behavior. *Trends Neurosci.* 1988;11:170–175.

Szentagothai J. The neuron network of the cerebral cortex: a functional interpretation. *Proc. R. Soc. Lond. B: Biol. Sci.* 1978;201:219–248.

Thompson RF, Krupa DJ. Organization of memory traces in the mammalian brain. *Annu. Rev. Neurosci.* 1994;17:519–549.

Turk DJ, Heatherton TF, Kelley WM, Funnell MG, Gazzaniga MS, Macrae CN. Mike or me? Self-recognition in a split-brain patient. *Nature Neurosci.* 2002;5:841–842.

Van Horn JD, Gazzaniga MS. Opinion: Databasing fMRI studies towards a discovery science' of brain function. *Nature Rev. Neurosci.* 2002; 3:314–318.

Xerri C, Merzenich MM, Jenkins W, Santucci S. Representational plasticity in cortical area 3b paralleling tactual-motor skill acquisition in adult monkeys. *Cereb. Cortex.* 1999;9:264–276.

Zeki S. *Inner Vision: An Exploration of Art and the Brain.* New York: Oxford University Press; 1999.

Index

A

Abducent nerve, 248, 250
Accessory cuneate nucleus, 232
Accessory nerve, 256, 257
Accommodation, 329
Acetylcholine (ACh),
  basal forebrain group projections, 269
  brainstem tegmental group projections, 269, 270
  metabolism, 268, 269
  neuromuscular junction synapse, 54, 56, 58, 269
  sympathetic nervous system, 353
Acetylcholine receptors,
  movement in plasma membrane, 19
  myasthenia gravis autoimmunity, 208, 210
  types, 269
ACh, *see* Acetylcholine
Action potential, 45–48, 52, 53
Active transport, 43
Adaptation,
  light, 333
  receptors, 177, 178
Adenosine, 282
Adrenal gland, 354
Afferent inhibition, 74
Aging,
  brain neuron loss, 101, 102, 119, 120
  neuron plasticity, 102, 103
Agnosias, 452
Agraphia, 451, 452
Alexia, 451
Allocortex, 439
Alpha motoneuron, 134, 141, 144, 151, 152, 194
ALS, *see* Amyotrophic lateral sclerosis
Alternating hemianesthesia, 306, 310
Alternating hemiplegia, 306, 307, 311, 312
Alveus, 391, 393
Alzheimer's disease, 460
Amblyopia, 125
γ-Aminobutyric acid (GABA), 15, 271, 414
Amygdala,
  anatomy, 395
  autonomic control, 364, 365
  circuitry, 395, 396
  learning and memory, 457, 459
  limbic system processing, 397–399
  nuclear groups, 398, 399
  overview, 2
  taste function, 265
Amyotrophic lateral sclerosis (ALS), 216
Anesthesia, 210
Angular gyrus, 449
Anomia aphasia, 451
Anopsia, 347
ANS, *see* Autonomic nervous system
Ansa lenticularis, 425
Anterior cerebral artery, 79, 83
Anterior choroidal artery, 79
Anterior spinal artery syndrome, 215
Anterior spinothalamic tract crude touch and movement sensation system (ASTT), 166, 182
Anterodorsal nucleus, 408
Anterograde transport, 116
Anterolateral pathway, 160, 225
Anteromedial nucleus, 408
Anteroventral nucleus, 408
Aphasias, 450–452
Apical dendrite, 440
Apoptosis,
  neurodegenerative disease, 119
  neuron development, 117, 118
  regulators, 119
Appetite, hypothalamic regulation, 380
Apraxia, 452
Aqueduct of Sylvius, 220
Aqueous humor, 330
Arachnoid, 89
Archicerebellum, 316
Arcuate nucleus, 233
Area postrema, 385
Argyll–Robertson pupil, 344

Aspiny neuron, 441
Association fibers, 440
Astereognosis, 191, 452
Asthenia, 326
Astrocyte, 28–30
ASTT, *see* Anterior spinothalamic tract
    crude touch and movement sensation system
Asynergia, 326
Ataxia, 191
Athetosis, 434
Auditory agnosia, 452
Auditory system,
  auditory cortex, 448, 449
  clinical considerations, 294, 295
  cochlear duct, 289, 290
  ear anatomy and physiology, 288, 289
  hair cells, 290–292
  pathways,
    ascending pathways, 292–294
    descending pathways, 294
    overview, 225
  sound reception, 289
Autonomic nervous system (ANS),
  cardiac nervous system, 358
  central control circuits, 363–367
  denervation sensitivity and sympathectomy, 367, 368
  enteric division, 356, 358, 359
  general organization, 351
  Hirschsprung's disease, 368
  parasympathetic division, 354, 356
  sensory and humoral systems,
    cotransmission, 363
    effector organ responses, 361, 363
    visceral sensory systems, 359, 361
  somatic motor system comparison, 349–351
  sympathetic division, 351, 353, 354
  urinary bladder control, 368
Axonal sprouting, 37
Axonal transport, 21, 23
Axon reaction, 33, 34

B

Babinski reflex, 212, 213
Ballism, 435
Barrington's nucleus, 368
Basal body, 291
Basal ganglia,
  circuits and connectivity,
    association circuit, 426
    core circuit, 423
    limbic circuits, 426, 528
    motor circuit, 423, 425, 426
    oculomotor circuit, 426
    substantia nigra, 428
    subthalamic nucleus, 428, 429
  nuclei, 429
  organization, 419–423, 429
  overview, 6, 419, 431, 432
  pathology, 433–436
  striatum,
    cell types, 429, 431
    patch-matrix compartments, 431
    ventral striatum, 421, 422
  ventral pallidum, 422, 423
Basal nucleus of Meynert, 390, 459
Basilar artery, 78
Basilar dendrite, 440
Basilar membrane, 289
Basilar pons, 219, 235
Basket cell somata, 317
Basolateral nuclear group (BLNG), 397–399
BBB, *see* Blood–brain barrier
BDNF, *see* Brain-derived neurotrophic factor
Benedikt's syndrome, 312, 313
Betz cell, 440
BLNG, *see* Basolateral nuclear group
Blood–brain barrier (BBB),
  carrier-mediated transport, 86
  diffusion, 86
  structure, 84, 86
Blood–cerebrospinal fluid barrier, 96, 97
Bouton, 11, 24
Brain, *see also specific regions*,
  brainstem, 9
  cerebrum, 2, 5–7, 9
  circulation,
    arterial supply, 78–81
    blood–brain barrier, 84, 86
    functional considerations, 81, 83

requirements, 77
venous drainage, 81
development,
cerebellum, 113, 114
congenital defects, 125
fetal development, 120–123
genetic factors, 124
nutrition, 124, 125
patterning, 105, 106
postnatal growth, 123, 124
nerve regeneration, 217
subdivisions, 1, 2
ventricles, 1, 90–92
weight, 1
Brain-derived neurotrophic factor (BDNF), 25
Brainstem,
blood supply, 307
cranial nerves, 9, 222, 223, 305
internal landmarks, 224–228
lesions, *see* Brainstem lesions
longitudinal organization, 219, 220
surface landmarks, 220–222
transverse sections, 228–242
Brainstem auditory evoked potential, 295
Brainstem lesions,
Benedikt's syndrome, 312, 313
cerebellopontine angle syndrome, 309, 310
medial longitudinal fasciculus, 310, 311
medulla,
medial zone, 307
posterolateral region, 307–309
Parinaud's syndrome, 313
pons,
lateral half of midpons, 311, 312
medial and basal portion of caudal pons, 310
unilateral lesions, 305, 306
Weber's syndrome, 312
Broca's aphasia, 451, 452
Brown Sequard syndrome, 213, 214
Bulbar palsy, 306

C

Caloric test, 302
Carbon monoxide (CO), 282
Carotid body reflex, 257
Carotid sinus reflex, 257
Cauda equina, 130
CCK, *see* Cholecystokinin
Central pain syndrome, 173
Central reticular nucleus, 230
Cerebellar ataxia, 191
Cerebellopontine angle syndrome, 309, 310
Cerebellum,
circuitry,
cerebrocerebrum, 324
inputs, 320, 321
internal feedback circuit, 325
outputs, 321
paravermal zone, 324
vermal zone, 323, 324
vestibulocerebellum, 324, 325
development, 113, 114
functional overview, 319–323
gross anatomy, 315
lesions and neurodegenerative disease, 325–327
peduncles, 221, 315, 320
proprioceptive pathways,
anterior spinocerebellar tract, 189
cuneocerebellar tract, 189
indirect pathways, 190
posterior spinocerebellar tract, 189
retrospinocerebellar tract, 189, 190
subdivisions,
cortex, 317–319
hemispheres, 315, 316
lobes, 315, 316
Cerebral cortex,
agnosias, 452
apraxia, 452
blood flow, 453, 454
dynamic maintenance, 460, 461
hemispheric dominance, 454–456
language and speech,
aphasias, 450–452
circuitry, 450, 451
learning and memory, 456–460
modular organization, 460
motor areas,
movement control, 446
premotor cortex, 443–445

primary motor cortex, 443
supplementary motor area, 445, 446
organization,
functional aspects, 443
neocortical neurons, 441–443
overview, 439, 440
prefrontal cortex, 452, 453
sensory areas,
auditory cortex, 448, 449
gustatory cortex, 447
plasticity, 449
somatosensory cortex, 446, 447
vestibular cortex, 447
visual cortex, 447, 448
split-brain subjects, 454–456
Cerebrocerebrum, 321, 324
Cerebrospinal fluid (CSF),
blood–cerebrospinal fluid barrier, 96, 97
clinical aspects, 98, 99
flow, 97
functions, 93, 94
hydrocephalus, 98
pressure, 97, 98
volume, 94, 96
Cerebrum,
basal ganglia, 6
diencephalon, 6, 7
gyri, 5, 6
hemispheres, 2
internal capsule, 7, 9
lobes, 2, 5
topography, 2, 5, 6
Chemesthesis, 157
Chemoreceptor, 157
Chief cell, 32
Cholecystokinin (CCK), 281
Chorea, 434
Choroid plexus, 96, 97
Cingulate gyrus, 396, 409
Circadian rhythm,
melatonin control, 383
overview, 381
sleep–wake cycle, 382, 383
suprachiasmatic nucleus control, 382
Circle of Willis, 79–81
Circumventricular organs, 98, 383–385
Cisterns, 89
Climbing fiber, 319
Clonus, 212
CMG, *see* Corticomedial nuclear group
CO, *see* Carbon monoxide
Coactivation, lower motoneurons, 151, 152
Cochlear duct, 286, 289, 290
Cochlear implant, 295
Collateral sprouting, nerves, 217
Coma, 311, 312
Combined system degeneration, 216
Commissural fibers, 440
Commissural interneuron, 152
Conductance, 42
Conductile segment, 50, 52, 53
Conduction aphasia, 451
Cone, 32, 331–333
Corpus callosum, 454–456
Corticobulbar tract, 200, 224, 419
Corticomedial nuclear group (CMG), 398, 399
Corticopontine tract, 224
Corticoreticulospinal pathway, 201
Corticorubral tract, 201
Corticorubrospinal pathway, 201
Corticospinal tract, 199, 200, 224, 419
Corticotectal tract, 202
Corticotropin-releasing hormone (CRH), 377
Cough reflex, 258
Cranial nerves, *see also specific nerves*,
brainstem nuclei, 246, 247
classification,
branchiometric nerves, 244, 245
general somatic afferent nerves, 244
special somatic afferent nerves, 243
ganglia in head, 246
motor nerves, 228
sensory nerves, 228
types, 9, 222, 223, 245
Cretinism, 125
CRH, *see* Corticotropin-releasing hormone
Crossed reflex, 143, 152
Crude touch, sensation pathways, 185, 187, 190, 191
Crus cerebri, 219, 240, 241, 415
CSF, *see* Cerebrospinal fluid
Cuneiform nuclei, 238, 241

Cuneocerebellar tract, 189

D

Deep tendon reflex, 143, 149, 214
Dendriole, 318
Dendrite,
  function, 68, 70, 71
  regulation, 71
  spines and synaptic plasticity, 116
  structure, 11, 23, 24
Dendrite–cell body unit, 50–52
Denticulate ligaments, 129
Depolarization, 45
Dermatomal vasodilatation, 211
Dermatome, 160
Diabetes insipidus, 380
Diencephalon, 1, 6, 7
Dissociated sensory loss, 211
DLF, *see* Dorsal longitudinal fasciculus
Dopamine,
  extrathalamic modulatory pathways, 415
  metabolism, 272, 273
  projections, 275–277
  prolactin release inhibition, 377
  reticular formation neurotransmission, 227, 228
  schizophrenia and dopamine hypothesis, 227
Dorsal column–medial lemniscus pathway, 182
Dorsal longitudinal fasciculus (DLF), 379
Dorsal motor vagal nucleus, 231
Dorsal root, 210, 211
Dorsal root ganglia, 130, 132
Dorsomedial nucleus, 261, 397, 409, 410
Down syndrome, 124
Ductus reuniens, 286
Dura mater, 89, 129
Dural sinuses, 81
Dysarthria, 327
Dysdiadochokinesis, 326
Dyskinesia, 433, 434
Dysmetria, 326

E

Ear, anatomy and physiology, 288, 289
Edinger–Westphal nucleus, 246, 342
EGF, *see* Epidermal growth factor
Emissary veins, 81
Endolymphatic duct, 287
Endolymphatic sac, 287
Endorphins, 172, 280
Enkephalins, 172, 280
Enterochromaffin cell, 32
Ependyma, 31, 32
Epidermal growth factor (EGF), 25
Epidural space, 129
Epinephrine,
  metabolism, 272, 273
  projections, 274, 275
EPSP, see Excitatory postsynaptic potential
Excitatory postsynaptic potential (EPSP), 47, 50–52, 63
Extended amygdala, 390, 391
Exteroceptor, 157
Extrapyramidal system, 200, 201
Eye,
  anatomy, 329
  movement,
    retinotectal pathways, 344, 345
    types, 345
  retina, 330, 331, 333, 335, 336

F

Facial colliculus, 221, 236, 237
Facial nerve, 252–254
Facial nucleus, 246
Fasciculation, 208
Fasciculi, 137, 138
Fasciculus cuneatus, 182
Fasciculus gracilis, 182
Fast-twitch fibers, 135
Feed-forward inhibition, 72–74
Feedback inhibition, 72–74
FGF, *see* Fibroblast growth factor
Fibrillation, muscle, 208
Fibroblast growth factor (FGF), 25
Fibronectin, 109
First messengers, 61–63
Fissures, cerebral, 2
Flexor reflex, 143, 150, 151
Flocculi, 316
Foramen of Magendie, 92
Foramina of Luschka, 92

Foramina of Monro, 81
Fornix, 391, 409

G

GABA, *see* γ-Aminobutyric acid
Gag reflex, 257, 258
Gamma motoneuron, 134, 141, 144, 149, 151, 152, 194
Gamma reflex loop, 149, 150
Gastric inhibitory peptide (GIP), 358
Gated ion channels, 45
General somatic afferent fibers, 132
General somatic efferent fibers, 133
General visceral afferent fibers, 132
General visceral efferent fibers, 133
Generator potential, 45–47, 49, 52
GHRH, *see* Growth hormone-releasing hormone
Gigantocellular reticular nucleus, 233, 234
GIP, *see* Gastric inhibitory peptide
Glial cell,
  astrocytes, 28–30
  classification, 28
  differentiation, 106, 107
  ependyma, 31, 32
  functions, 27, 28
  microglia, 30, 31
  oligodendrocytes, 30
  Schwann cells, 32
  Global aphasia, 451
Glomerulus, 317
Glossopharyngeal nerve, 234, 254
Glucagon, 280
Glucostat hypothesis, 380
Glutamate, 271, 272, 414, 415
Glycine, 271
GnRH, *see* Gonadotropin-releasing hormone
Golgi cell, 317
Golgi tendon organ (GTO), 143, 146, 150, 153
Golgi tendon reflexes, 143
Gonadotropin-releasing hormone (GnRH), 377
G-proteins, 63, 267
Graded potential, 45–47
Granule cell, 317
Great vein of Galen, 81
Growth cone, 109
Growth hormone-releasing hormone (GHRH), 377
GTO, *see* Golgi tendon organ
Guidepost cell, 109
Gustation,
  central taste pathway, 264, 265
  gustatory cortex, 447
  gustatory nucleus, 264
  pathways, 262–265
  taste buds, 262
  taste modalities, 262, 264

H

Hair cells,
  auditory, 290–292
  overview, 32
  vestibular, 296, 298
Helicotrema, 286
Hemianopsia, 346, 347
Hemiplegia, 212
Heteronymous muscle, 149
Hippocampal formation, 391–393
Hippocampus,
  Korsakoff's syndrome, 403
  learning and memory, 459
  overview, 2
Hirschsprung's disease, 368
Histamine, 415
Homonymous muscle, 149
Horizontal cell of Cajal, 442
Horner's syndrome, 210
Huntington's disease, 271, 419, 434, 436
Hydrocephalus, types, 98
Hyperalgesia, 210
Hyperpolarization, 45
Hyperreflexia, 208, 212
Hypertonia, 151, 212
Hypesthesia, 210
Hypoglossal nerve, 246, 258
Hypoglossal nucleus, 231
Hypothalamus,
  autonomic control, 363, 364, 378, 379
  behavioral regulation, 380, 381
  circadian rhythm control,
    melatonin, 383
    overview, 381
    sleep–wake cycle, 382, 383

suprachiasmatic nucleus, 382
circuitry,
inputs, 376
outputs, 376
food intake and energy balance regulation, 380
functional overview, 371–373, 375
intrinsic receptors, 375
neurohumoral reflexes, 375–378
releasing and inhibiting hormones, 375, 377, 378
temperature regulation, 379
water balance regulation, 379, 380
Hypotonia, 151, 208, 326

I

Incus, 289
Inferior colliculus, 220, 238, 239
Inferior olivary complex, 232–234
Inferior salivatory nucleus, 246
Inferotemporal cortex, 448
Inhibitory postsynaptic potential (IPSP), 47, 50–52, 63
Initial segment, 49, 50, 52
Integrated potential, 52
Internal arcuate fibers, 230, 231
Internal capsule, 415, 415
Internal carotid artery, 79
Internal jugular veins, 81
Interneurons,
integration of spinal reflexes, 152, 153
lateral inhibition, 268
Internuclear ophthalmoplegia, 310, 311
Interoceptor, 157
Interpeduncular nucleus, 241
Intersegmental interneuron, 152, 196
Intersegmental reflex, 143
Interstitial nucleus of Cajal, 241
IPSP, *see* Inhibitory postsynaptic potential
Itching, 171

J

Jaw jerk reflex, 187, 188
Juxtarestiform body, 234

K

Kinesthetic sense, 177
Klüver–Bucy syndrome, 402, 403
Korsakoff's syndrome, 403

L

Labyrinths,
membranous labyrinth, 285, 287
osseus labyrinth, 285, 286
sensory receptor areas, 288
Laminin, 109
Language,
aphasias, 450–452
circuitry, 450, 451
Large aspiny neuron, 431
Lateral dorsal nucleus, 413
Lateral geniculate body (LGB), 412, 413
Lateral geniculate nucleus (LGN), 337
Lateral inhibition, 268
Lateral lemniscus, 237
Lateral posterior nucleus, 413
Lateral reticular nucleus, 232
Lateral reticular zone, 234
Lateral spinothalamic tract pain and temperature system (LSTT), 165, 166, 174
Lateral tegmental receptor field (LTF), 364–367
Learning, 456–460
Lenticular fasciculus, 25
Leptomeninges, 89
LGB, *see* Lateral geniculate body
LGN, *see* Lateral geniculate nucleus
Limbic system,
amygdala, 395–399
basal nucleus of Meynert, 390
circuitry, 395–397
electrical stimulation studies, 401, 402
extended amygdala, 390, 391
functional overview, 387, 390
hippocampal formation, 391–393
Klüver–Bucy syndrome, 402, 403
Korsakoff's syndrome, 403
limbic lobe, 439
Papez circuit, 393
processing triangle, 397
reinforcement and reward centers, 402
schizophrenia defects, 400, 401
subdivisions,
amygdala pathway, 394, 395
caudal limbic system, 395

mesocorticolimbic system, 395, 399, 400
mesolimbic system, 395, 399, 400
overview, 393, 394
rostral limbic system, 395
septal pathway, 394
substantia innominata, 390
Locus ceruleus,
norepinephrine projections, 275
overview, 238
spinal pathway, 202, 203
Long circumferential arteries, 79
Lower motor neurons,
alpha motoneurons, 134, 141, 144, 151, 152, 194
cell bodies, 194–196
functions, 193, 194
gamma motoneurons, 134, 141, 144, 149, 151, 152, 194
LSTT, *see* Lateral spinothalamic tract pain and temperature system
LTF, *see* Lateral tegmental receptor field
Lumbar puncture, 98

M

Macula, 331
Magnocellular pathway, 341, 342
Malleus, 289
Mamilothalamic tract, 408
Martinotti cell, 442
Mechanoreceptor, 157, 160, 177, 178, 180
Medial geniculate body (MGB), 412
Medial lemniscus decussation, 230–232
Medial longitudinal fasciculus (MLF), 202, 225, 310, 311
Medium spiny neuron, 429, 431
Medulla,
autonomic control,
cardiovascular function, 366, 367
functional neuroanatomy, 365, 366
lateral tegmental receptor field, 364–367
lesions,
medial zone, 307
posterolateral region, 307–309
overview, 1, 9
pyramids, 219
Meissner corpuscle, 178
Melanocyte-stimulating hormone release-inhibiting factor (MIF), 377
Melanocyte-stimulating hormone-releasing factor (MRF), 377
Melatonin, 383
Memory, 456–460
Meniere's disease, 300
Meninges, 89, 90, 129
Merkel cell, 32
Merkel disk, 178
Mesencephalic nucleus of the trigeminal nerve, 187, 188
Mesencephalon, 1
Mesocortex, 439
Metencephalon, 1
N-Methyl-D-aspartate (NMDA), 272
MGB, *see* Medial geniculate body
Microglia, 30, 31
Middle cerebral artery, 79, 83
Middle-ear reflex, 295
MIF, *see* Melanocyte-stimulating hormone release-inhibiting factor
MLF, *see* Medial longitudinal fasciculus
Monosynaptic reflex, 143
Mossy fiber, 320
Motion sickness, 302
Motor neurons, *see* Lower motor neurons; Upper motor neurons
Motor pathways,
corticobulbar tract, 200
corticoreticulospinal pathway, 201
corticorubrospinal pathway, 201
corticospinal tract, 199, 200
corticotectal tract, 202
extrapyramidal system, 200, 201
functional groups of descending pathways, 203, 204
locus ceruleus–spinal pathway, 202, 203
medial longitudinal fasciculus, 202
raphe–spinal pathway, 202, 203
tectobulbar tract, 202
tectospinal tract, 202
vestibulospinal tract, 202
Movement, sensation pathways, 185, 187
MRF, *see* Melanocyte-stimulating hormone-releasing factor

Muscle spindles, 143–146, 149
Muscle tone, 151
Myasthenia gravis, 208, 210
Myelencephalon, 1
Myotome, 134

N

NCAMs, *see* Neural cell adhesion molecules
Negative feedback loop, 65
Neocerebellum, 317, 326
Neocortex, *see* Cerebral cortex
Nernst equation, 43, 44
Nerve growth factor (NGF), 25, 109
Netrins, 111
Neural cell adhesion molecules (NCAMs), 112
Neural crest, 105
Neural fold, 103
Neural plate, 103
Neural stem cell (NSC),
  development, 107, 108
  therapeutic prospects, 108
Neural tube, 103, 105
Neurofibrillary tangles, 460
Neurogenic hyperthermia, 379
Neuromodulators, 64
Neuromuscular junction (NMJ),
  structure, 67
  synapse, 54, 56, 58
Neuron,
  axonal transport, 21, 23
  components,
    cytoskeleton, 21
    dendrites, 23, 24
    endoplasmic reticulum, 19, 20
    Golgi apparatus, 20, 21
    lysosomes, 20
    mitochondria, 20
    Nissl bodies, 19
    nucleus, 11, 14, 15, 17
    peroxisomes, 20
    plasma membrane, 17–19
    ribosomes, 19
  development,
    activity-dependent and experience-dependent stage, 113
    apoptosis, 117–119
    differentiation, 106, 107
    navigation and docking, 108, 109, 111–113
  electrophysiology,
    action potential, 45–48, 52, 53
    coding and processing in nervous system, 71, 72, 74
    dendrite function, 68, 70, 71
    excitability, 44, 45
    functional organization, 48–50
    graded potential, 45–47
    integrated potential, 52
    messenger systems, 61–64
    Nernst equation, 43, 44
    receptor potentials, 50–52
    resting potential, 41–43
    stimuli integration, 65–67
  neurotransmission, 58–61
  neurotrophic factors, 24, 25
  peripheral nerves, 26
  plasticity, *see* Plasticity, neurons
  protein synthesis, 14, 15
  regeneration,
    axon reaction, 33, 34
    central nervous system, 36
    collateral sprouting, 35
    peripheral nervous system, 34, 35
    spinal cord, 36, 37
  synapse,
    chemical, 53, 54, 56, 58
    electric, 64, 65
    structure, 24
Neuropeptides, 278–281
Neuropeptide Y (NPY), 281, 363
Neurotensin, 281
Neurotransmitters, *see also specific transmitters,*
  receptor interactions, 59, 60
  storage and release, 59
  synapse activity, 61
  synaptic vesicle removal and recycling, 60
  synthesis, 58, 59
  types, 58, 268
Neurotrophins, 25
NGF, *see* Nerve growth factor
Nitric oxide (NO), 281, 282

NMDA, *see N*-Methyl-D-aspartate
NMJ, *see* Neuromuscular junction
NO, *see* Nitric oxide
Nociception, *see* Pain
Node of Ranvier, 26
Nodulus, 316, 327
Norepinephrine,
  extrathalamic modulatory pathways, 415
  metabolism, 272, 273
  projections, 273–275
  reticular formation neurotransmission, 227
  sympathetic nervous system, 353, 354
NPY, *see* Neuropeptide Y
NSC, *see* Neural stem cell
Nucleus accumbens, 397, 399
Nucleus ambiguus, 231, 246
Nucleus gracilis, 229, 230
Nucleus interpositus, 234
Nucleus of Darkschewitsch, 241
Nucleus of the inferior colliculus, 238
Nucleus reticularis pontis oralis, 238
Nucleus ruber, 241
Nucleus solitarius, 231, 246, 264
Nystagmus, 300

O

Oculomotor nerve, 246, 248–250
Oculomotor nuclear complex, 240
Olfaction,
  accessory olfactory system, 261, 262
  olfactory receptor neurons, 259
  overview, 258
  pathways, 259, 260
  refinement and neural processing, 259, 261
  uncinate fit, 261
Olfactory nerve, 247, 248
Olfactory receptor cell, 32
Oligodendrocyte, 30
Olivary complex, 232–234
Ophthalmic artery, 79
Opioid peptides, 280
Optic chiasma, 346
Optic disk, 345, 346
Optic nerve, 248
Organ of Corti, 290–292
Organum vasculosum of the lamina terminalis (OVLT), 385
Oval window, 289
OVLT, *see* Organum vasculosum of the lamina terminalis
Oxytocin, 281

P

Pacinian corpuscle, 178
PAG, *see* Periaqueductal gray
Pain,
  afferent first-order neurons, 159, 160
  central pain syndrome, 173
  central perception, 170, 171
  dermatomes, 160
  modulation,
    descending control mechanisms, 171, 172
    endogenous pain control, 172
    gate control theory, 171
  nociceptors, 158, 159
  pathways from anterior head, 169, 170
  pathways from body, limbs, and back of head, 160, 162–165
  phantom limb sensation, 173, 174
  referred pain, 172, 173
  spinal cord neurons and ascending projections,
    functional considerations, 165
    spinothalamic and trigeminothalamic pain pathways, 165, 166
    types of neurons, 165
  stress induced analgesia, 173
  Wall's concept of pain and target motor responses, 166, 168
Paleocerebellum, 316
Paleospinothalamic pathway, 164
Papez circuit, 393
Parabrachial nucleus, 364
Parafascicular nucleus, 413
Paramedian arteries, 79
Paramedian reticular nuclei, 233
Paraneurons, types, 32, 33
Paraplegia, 214
Paresthesia, 210
Parinaud's syndrome, 313
Parkinson's disease, 419, 433, 434, 436

Pars caudalis, 170
Pars interpolaris, 170
Pars oralis, 170
Parvicellular reticular nucleus, 234
Parvocellular pathway, 341, 342
Passive diffusion, 43
Pattern code, 72
Pedunculopontine nuclei, 238
Periaqueductal gray (PAG), 171, 172
Peristaltic reflex, 358, 359
Periventricular tract, 364
PET, *see* Positron emission tomography
Phantom limb sensation, 173, 174
Phenylketonuria (PKU), 124
Pheromones, 262
Pia mater, 89
Pituitary gland,
  anatomy, 371
  hypothalamic regulation, 375–378
  neurohypophysis as circumventricular organ, 384, 385
PKU, *see* Phenylketonuria
Placode, 103
Plasticity, neurons,
  aging brain, 102, 103
  chemical, 115
  cortical columns, 449
  developmental, 115
  neuronal, 115
  neurotrophic-derived, 115
  overview, 11, 37, 114
  synaptic, 115, 116
Polysynaptic reflex, 143
Pons,
  lesions,
    lateral half of midpons, 311, 312
    medial and basal portion of caudal pons, 310
  overview, 1, 9
Pontine micturition center, 368
Pontocerebellar tract, 225
Positron emission tomography (PET), 77, 325, 397, 443
Posterior cerebral arteries, 78
Posterior column–medial lemniscus pathway, 224
Posterior communicating artery, 79
Posterior thalamic nucleus, 413
Prefrontal cortex, 452, 453
Premotor cortex, 199, 443–445
Presbycusis, 294, 295
Presynaptic facilitation, 67
Presynaptic inhibition, 67, 68
Pretectum, 221
Primary motor cortex, 196, 198, 199
Prion disease, 327
Projection fibers, 440
Proprioception, *see also* Vestibular system,
  cerebellar pathways, 189, 190
  discriminatory general sensory pathway,
    overview, 180–183
    paths from receptors to cortical columns, 183, 185
    thalamus and somatosensory cortex, 183
  head pathways, 187, 188
  overview, 142, 155, 156, 180
  pathology, 190, 191
  proprioceptors, 157
  trigeminothalamic pathway, 185
Pseudobulbar palsy, 306, 312
Ptosis, 312
Pulvinar, 413
Purkinje cell, 317–319
Pyramidal cell, 440
Pyramidal decussation, 229, 230

Q, R

Quadriplegia, 214, 215
Radicular arteries, 130
Raphe nuclei, 238
Raphe–spinal pathway, 202, 203
Rebound phenomenon, 326
Receptive segment, 49–52
Red nucleus, 239, 240
Referred pain, 172, 173
Reflected excitation, 74
Reflected inhibition, 74
Reissner's membrane, 289
Release phenomenon, 207, 325
Renshaw cell, 65, 152
Resting potential, 41–43
Reticular formation (RF),
  anatomy, 387, 388

circuitry, 388–390
functional overview, 387–390
neurotransmission,
dopaminergic system, 227, 228
noradrenergic system, 227
serotonergic system, 227
structure, 225, 226
Reticular nuclei, 232, 406, 407
Reticulospinal tract, 201
Reticulotegmental nucleus, 238
Retina,
adaptation, 333
bipolar cells, 336
cell types, 330, 331
information flow, 330, 331
retinal ganglion cells, 333, 335, 336
rods and cones, 331–333
Retinogeniculostriate pathway, 337
Retrograde transport, 117
Retrospinocerebellar tract, 189, 190
Rexed's laminae, 136
RF, *see* Reticular formation
Rhombencephalon, 105
Rigidity, 151
Rod, 331–333
Romberg's sign, 191
Rostral ventrolateral reticular nucleus, 363, 364
Rotation test, 302
Rubrospinal tract, 201
Ruffini corpuscle, 180

S

Saccule, 296
Scala media, 286, 289, 290
Scala tympani, 286
Scala vestibuli, 286
Schizophrenia,
dopamine hypothesis, 227
limbic system defects, 400, 401
Schwann cell, 26, 27, 32, 117
SCN, *see* Suprachiasmatic nucleus
Scotoma, 345
Second messengers, 62, 63
Secretin, 280
Segmental reflex, 143
Senile plaque, 460
Sensorineural hearing loss, 294
Sensory systems,
overview of features, 156, 157
pathways,
first-order neurons, 159, 160
second-order neurons, 162–164
third-order neurons, 164, 165
receptors, 156–159
Serotonin,
metabolism, 272, 273
projections, 277, 278
Serotonin,
extrathalamic modulatory pathways, 415
reticular formation neurotransmission, 227
Shell neuron, 183
Short circumferential arteries, 79
Signal-line code, 71, 72
Sleep–wake cycle, *see* Circadian rhythm
Slow-twitch fiber, 134
Sodium/potassium-ATPase, 42, 43
Solitary nucleus, 363
Somatic motor system, organization, 142, 143
Somatosensory cortex, 183, 446, 447, 454
Somatostatin, 281, 377
Spastic paralysis, 212
Spina bifida, 126
Spinal cord,
blood supply, 130, 215
development, 105, 106, 120
dorsal roots, 130, 132, 133
first cervical segment, 229
laminae, 136, 137
lesions, *see* Spinal cord lesions
meningeal coverings, 129
nerve components, 130
pathways and tracts, 137–139
regeneration, 36, 37, 217
spina bifida, 126
ventral roots, 133–136
Spinal cord lesions,
amyotrophic lateral sclerosis, 216
combined system degeneration, 216
crude touch sensation, 191
degeneration, 216, 217
dorsal roots, 210, 211
hemisection, 213, 214
localization, 213

release phenomenon, 207
syringomyelia, 215, 216
tabes dorsalis, 216
transection,
paraplegia, 214
quadriplegia, 214, 215
upper motor neurons, 211–213
ventral roots, 207, 208, 210
Spinal reflex arcs, 143
Spinal reflex responses, 141, 142
Spinocerebellar tract, 189, 225
Spinocerebellum, 316, 321
Spinocervicocerebellar pathway, 190
Spinocervicothalamic pathway, 187
Spinomesencephalic tract, 160, 164
Spinoolivary tract, 190
Spinoreticular tract, 160, 14
Spinoreticulothalamic pathway, 164
Spinospinal fasciculi, 138
Spinothalamic tract, 160, 162, 174
Spiny stellate cell, 441
Stapedius, 289
Stapes, 289
Stellate cells, 317, 440, 441
Stereocilia, 291
Strabismus, 312
Stretch receptors, 144
Stretch reflex, *see* Deep tendon reflex
Striatum, *see* Basal ganglia
Stroke, infarct sites, 83
Subcommissural organ, 385
Subfornical organ, 385
Substance P, 281
Substantia innominata, 390
Substantia nigra, 240, 428
Subthalamic nucleus, 428, 429
Superior central nucleus, 238
Superior cerebellar peduncle, 237, 238
Superior colliculus, 220, 239–241, 313
Superior olivary complex, 237, 292, 293
Superior salivatory nucleus, 246
Superior vestibular nucleus, 236
Supplementary motor area, 199, 445, 446
Suprachiasmatic nucleus (SCN), 382
Supramarginal gyrus, 449, 452
Supranuclear facial palsy, 253, 254
Supraopticohypophyseal tract, 375, 378
Synapse,
chemical, 53, 54, 56, 58
electric, 64, 65
structure, 24
types, 66, 67
Synaptic bombardment, 65
Synaptic potential, 45–47, 49–52
Synaptic vesicle, removal and recycling, 60
Syringomyelia, 215, 216

T

Tabes dorsalis, 216
Tactile disorders, 190
Tardive dyskinesia, 434
Taste, *see* Gustation
Taste buds, 262
Taste receptor cell, 32, 262, 263
Taste–salivary gland reflex, 257
Tectobulbar tract, 202
Tectorial membrane, 291
Tectospinal tract, 202
Tectum, 219, 220
Tegmentum, 219, 234
Telencephalon, 1
Temperature,
hypothalamic regulation, 379
perception,
pathways from anterior head, 169, 170
pathways from body, limbs, and back of head, 160, 162–165
thermoreceptors, 157–159, 170
Temporal lobe, 457, 459
Tensor tympani, 289
Thalamic syndrome, 173
Thalamus,
drivers and modulators, 405, 406
extrathalamic modulatory pathways, 415
functional overview, 405, 416
internal capsule, 415, 416
lesions, 417
limbic thalamus, 414
morphology, 407, 408
neuron types, 408
neurotransmitters, 414, 415
nuclei,
anterior nuclear group, 408, 409
classification, 408
intralaminar nuclear group, 413, 414
lateral nuclear group, 413

medial nuclear group, 409, 410
midline nuclear group, 414
organization, 407, 408
posterior nuclear group, 413
ventral nuclear group, 410–413
reticular nucleus, 406, 407
Thermoreceptor, 157–159
Thermostat hypothesis, 380
Thyrotropin-releasing hormone, 281, 377
Tinnitus, 294
Titubation, 327
Tract of Lissauer, 160
Transmissive segment, 50, 53, 54, 56, 58
Tremor, 325, 326
Trigeminal nerve,
lesion, 252
midpontine level, 237, 238
motor root, 251, 252
nuclei, 231, 237, 241, 245
pathways, 225
sensory root, 250, 251
Trigeminoreticulothalamic pathway, 170
Trigeminothalamic pathway, 185, 231, 238
Trochlear nerve, 246, 248, 250
Trophic segment, 50
Tuber cinereum, median eminence, 384
Tuberohypophyseal tract, 377
Tympanic membrane, 288

U

Uncinate fit, 261
Unipolar brush cell, 317, 318, 320
Upper motor neuron,
function, 196
lesions, 211–213
Utricle, 296

V

Vagus nerve,
dorsal motor nucleus, 247
function, 254, 255
lesion, 255, 256
Vasoactive intestinal polypeptide (VIP), 279–281, 363
Vasopressin, 281, 380
Ventral anterior nucleus, 410, 411
Ventral lateral nucleus, 412
Ventral medial nucleus, 413
Ventral pallidum, 422, 423, 446
Ventral pons, 234
Ventral posterior nucleus, 412
Ventral posterolateral nucleus of the thalamus, 182, 183
Ventral posteromedial nucleus, 264
Ventral root, lesions, 207, 208, 210
Ventral striatum, 421, 422, 446
Ventricles, 1, 2, 90–92
Vermis, 315
Vertebral arteries, 78
Vertigo, 300, 302
Vestibular cortex, 447
Vestibular system,
hair cells, 296, 298
labyrinths,
membranous labyrinth, 285, 287
osseus labyrinth, 285, 286
sensory receptor areas, 288
postural pathways, 299, 300
saccule, 296
tests and disorders, 300, 302
utricle, 296
vestibular nuclei,
inputs, 298, 299
outputs, 299
vestibuloocular pathways, 300
Vestibulocerebellum, 316, 321, 324, 325
Vestibulocochlear nerve, 234, 254
Vestibuloocular reflex (VOR), 345
Vestibulospinal tract, 202
VIP, *see* Vasoactive intestinal polypeptide
Visual agnosia, 452
Visual cortex, 447, 448
Visual system,
eye,
anatomy, 329
movement,
retinotectal pathways, 344, 345
types, 345
retina, 330, 331, 333, 335, 336
lesions, 345–347
magnocellular pathway, 341, 342
parvocellular pathway, 341, 342

reflex pathways,
accommodation–convergence reaction circuit, 344
accommodation reflex circuit, 344
Argyll–Robertson pupil, 344
pupillary dilatation circuit, 344
pupillary light reflex pathway, 342, 344
retinogeniculostriate pathway, 337
retinotopic representation of visual fields, 337
visual cortex,
primary visual cortex, 337, 339, 340
visual association areas, 340, 341
Vitreous humor, 330
VNO, *see* Vomeronasal organ
Voluntary movement, control, 204, 205
Vomeronasal organ (VNO), 261, 262
VOR, *see* Vestibuloocular reflex

W

Wallenberg's syndrome, 307
Water balance, hypothalamic regulation, 379, 380
Weber's syndrome, 312
Wernicke's aphasia, 450, 451
Wernicke's area, 449–451